STUDIES IN THE AETIOLOGY OF ECLAMPSIA AND THE ALBUMINURIA OF PREGNANCY WITH SPECIAL REFERENCE TO THE PLACENTAL THEORY.

by

DOUGLAS MILLER, M.B., Ch.B.

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I N T R O D U C T I O N.

Among the unsolved problems of obstetrics, none is of greater interest or calls more urgently for solution than eclampsia. Since the discovery by Lever, in 1843, of albumen in the urine of eclamptic patients an immense literature has accumulated round the subject - the year 1908 alone producing considerably over one hundred scientific papers dealing with it - and so numerous have been the views advanced that the condition well merits the title of "the disease of theories" given it by Zweifel. The explanation of the amount of work done is to be sought partly in the baffling nature of the problem and partly in the advances that have been made in our knowledge of the general metabolism of the body, the theories of immunity, the action of intracellular ferments, and the physiology of the ductless glands. Within recent years the majority of investigations have pointed to the placenta as the most probable source of the "poison". It is with the placental theory that this thesis is principally concerned; in particular I have attempted to afford confirmation of the view advanced by James Young in 1914 as to the aetiological importance of placental infarction in eclampsia and the albuminurias of pregnancy.

The investigation has been carried out along clinical, pathological, and experimental lines; the material for the first of these consisted in a consecutive series of fifty-five cases of toxaemia or of antepartum haemorrhage, observed for the main part in the Wards of the Royal Maternity Hospital, to the physicians of which my thanks are due for facilities afforded. The pathological line of enquiry concerned itself mainly with the observation of morbid changes present in the placenta, an attempt being made to correlate the appearances present with the clinical findings. Finally a series of animal experiments was conducted, so that conclusions to which the preliminary investigations had led might be modified or confirmed.

The thesis is presented in two parts; the first part is devoted to a critical review of the literature dealing with the more important theories of eclampsia; in the second, the "infarction" theory is considered in the light of cases observed and experiments performed.

A number of coloured plates and micro-photographs are submitted in a separate volume.

For the loan of plates II, III, and IV my thanks are due to Dr Fordyce.

I would also thank Dr James Young for much help and advice. My indebtedness to him is insufficiently indicated by the frequent recurrence of his name in the text.

PART I.

In strange contrast to the completeness of our knowledge along clinical lines, the paucity of facts bearing upon the etiology of eclampsia is indeed striking. Moreover the investigations which have been undertaken have brought forth so many apparent contradictions that in attempting to gain information of value from the contributions made, a serious difficulty has been to distinguish good work from bad.

It would be beyond the compass of this paper even to mention all the theories from time to time advanced, and in the following pages attention will be directed only to those views which have attracted greatest interest and which seem to have most significance from the writer's point of view.

The theories which have appeared worthy of consideration are the following.- 1. Metabolic Autointoxication. 2. Bacterial. 3. Abberation in function of the Ductless Glands. 4. Mechanical. 5. Anaphylaxis. 6. Placental.

I. METABOLIC/

I. METABOLIC AUTO-INTOXICATION.

Rivière in 1888 was the first to suggest that eclampsia was an auto-intoxication, its presence being shewn by an increase in the toxicity of the blood serum and a decrease in that of the urine. By the term metabolic auto-intoxication is understood the disturbance produced by products of metabolism which have been formed within the tissues. A harmful accumulation of metabolic products or an auto-intoxication may result from any of the following conditions (Wells).

(1) Failure of elimination because of abnormal conditions in the eliminating organs, e.g. uraemia.

(2) Failure of neutralisation by chemical combination, presumably due to abnormalities in the organs or tissues through whose activities the neutralisation is normally accomplished, e.g. diseases of the liver.

(3) Failure of the chemical transformation of the metabolic products; this may result either from abnormalities in the functioning tissues or through a checking of the normal steps of metabolism by failure of elimination of the end products.

(4)/

(4) Excessive formation of toxic chemical substances, e.g. autolytic changes in an organ such as the liver.

It is impossible to classify eclampsia under any of the above headings, but so complex and so far reaching are the anatomical and chemical changes met with, that probably all four may be looked on as factors of importance.

That the process of building up a foetus of six or seven pounds weight, as well as the provision of a suitable lodging for it by the growth of the uterus, must inevitably lead to an increased metabolism is natural. Accurate measurement of the degree of increased metabolism has been made possible by the introduction of the measurement of the basal metabolism rate. This may be defined as the measurement of the energy metabolism of the individual at complete rest and in the post-absorptive state (Baer). It is determined by ascertaining the heat production or gaseous interchange in such a subject during a certain period and expressed in calories per kilogram of body weight. The investigations of Baer in forty-four carefully studied cases of pregnancy show a gradual rise from + 26 in the thirty-fourth week, to + 33 in the fortieth week, dropping to + 15 on the third day/

day after labour, to + 5 on the seventh day, and becoming normal on the fifteenth day of the puerperium. These are average figures and refer to normal cases. Two further cases observed by Baer, which shewed symmetrical thyroid enlargement without symptoms, gave figures below the series average in metabolic rate, which appears to support the view as to the primarily compensatory nature of thyroid enlargement during pregnancy. In five cases of eclampsia the metabolic rate was also determined; in only two of these was variation from the average figure noted, though in what direction is not indicated.

Granted that there is an increased metabolism during pregnancy, the strain of this must inevitably fall on such organs as the liver and kidney, especially the former. Expressed in simple language, the hypothesis advanced by those who seek to find in disordered metabolism an explanation of the phenomena of eclampsia, is that an auto-intoxication results through failure of the elaborate system of defence with which the body is provided to deal with the more or less toxic waste products resulting from an increased metabolism. What the exact nature of this auto-intoxication is, and the processes by which it is brought about involve problems of bio-chemistry extremely/

extremely complex and baffling for the average obstetrician, the more confusing as contributions of different observers giving the results of blood and urine analysis, and of tests of renal and hepatic functional efficiency have not always been in agreement.

The rôle which the foetus may play will be dealt with in a later section, meantime it may be asserted that of possible toxic products of foetal metabolism we have as yet no definite knowledge, nor do we know to what extent foetal metabolism throws an additional strain on the maternal excretory organs.

No clue as to the ultimate cause of the disease has been forthcoming from research on the disordered metabolism which accompanies eclampsia; and hopes that by blood and urine analysis not only could the tissue changes be satisfactorily explained, but even the toxin or group of toxins responsible be isolated, have proved abortive. As the ultimate solution of the problem, however, will probably be arrived at along lines of biochemical research, an outline of recent work done is warranted here. The observations made can be conveniently recorded under the following headings: (1) The Acidosis factor. (2) Renal and Hepatic function in eclampsia.* (3) The rôle of alimentation.

* For much information with regard to recent research on acidosis, and on renal and hepatic function in eclampsia I am indebted to De Wesselow's valuable critical review.

1. Acidosis. By acidosis is understood a condition in which an abnormal quantity of organic acids escapesoxidation and remain free in the body where they may be detected in the blood and urine. Work on acidosis as the cause of the toxaemias of pregnancy dates back to the investigations of Zangemeister who in 1903 estimated the alkalinity of the blood in normal pregnancy and eclampsia and found it slightly reduced in the latter. In the following year Zweifel offered his theory that eclampsia resulted from over-production of lactic acid of the foetus.* More recently Ewing and Wolf, finding leucine and tyrosine in the urine, suggested that amino-acids, incompletely catabolised in the liver, were actually the cause of the toxaemia and the abnormal nitrogen distribution. Hasselbach and Gammeltoft in 1915 from a careful study of ten pregnant women came to the conclusion that in normal pregnancy a slight acidosis is present. They found that during the course of pregnancy the ammonia-coefficient rose steadily and that this rise was accompanied by a corresponding fall in the alveolar CO_2 tension. Later, Slemons, Einge, Losee and Van Slyke investigated the/

* The injection of lactic acid into animals causes no disturbance. It is probably a disintegration product of proteid and of no special significance.

the alkaline reserve of the blood plasma by testing the CO_2 combining power of the blood plasma. They found it reduced and corroborated the results of Hasselbach and Gammeltoft that in pregnant women a slight acidosis is normally present. The same observers carried out a similar blood investigation in eclampsia and the pre-eclamptic state and found figures practically within normal limits. As far as a state of acidosis can be determined by blood analysis, the slight and constant diminution in the alkaline reserve of the plasma does not support the view that acidosis should be looked on as the underlying cause of toxaemia in the later months of pregnancy. Analysis of the urine, moreover, judging from the figures of Ewing and Wolf and later of Slemons, Losee and Van Slyke, shews a comparatively small rise in the ammonia-coefficient in cases of eclampsia as distinct from hyperemesis, a finding which supports the same view.

2. Renal and Hepatic function.

Since the investigations of Gscheidlin and Spiegelberg (1870) who estimated the urea and ammonium carbonate in the blood, and Butte (1894) who estimated the urea in the blood, methods of testing renal function have advanced considerably, and in investigating renal impairment have been applied widely without adding/

adding very materially to our knowledge of the nature of eclampsia. The normal level of the blood urea in pregnancy is disputed. Folin (1912) from an investigation of 100 cases states that the blood urea is abnormally low. Losee on the other hand found figures similar to those of non-pregnant individuals. Herter, Zangemeister, Farr, and P.F. Williams have reported the blood urea and the total non-protein nitrogen of the blood normal or only slightly increased in women suffering from eclamptic toxaemia. Losee recently reported the creatinin blood content of 13 patients with eclampsia between 1.45 and 3.15 mg. per 100 cc., figures only slightly above normal.

Lisle Williams (1921) has drawn attention to the increase in uric acid in the blood of toxaemic patients. With the exception of Slemons and Bogert (1917), who reported uric acid in excess of normal in the blood of two patients with eclampsia and three with pre-eclamptic toxaemia, there were few references in the literature concerning the uric acid blood content of pregnant women, especially those with symptoms of toxaemia, before Williams paper appeared. Williams carried out a chemical analysis of the blood of twenty-five patients suffering from different types of pregnancy toxaemia and demonstrated that in the blood of/

NON-PROTEIN NITROGEN CONSTITUENTS - mg. per 100 cc.

		Urea N.	Non-protein N.	Uric acid.	Creatinin.
Group I.	Eclampsia: 5 cases. Average.	17.2	40.1	7.84	2.67
Group II.	Pre-eclamptic toxaemia: 13 cases. Average.	15.8	31.9	3.9	1.57
Group III.	Normal Pregnancy at various months. Average.	12.76	26.68	1.94	1.38
Non-pregnant individuals.		12-23	20-35	1.3 - 3	0.7 - 1.5

A group of seven cases of pernicious vomiting has not been included.

of these patients the amount of uric acid regularly exceeds the normal, whereas the other non-protein nitrogen constituents are not usually increased. His table is of sufficient interest to reproduce.
Lisle Williams lays great stress on uric acid excess; he suggests absorption of foetal urine as a possible source.

The diastase content of the urine has been dealt with specially by Mackenzie Wallis.* In normal pregnancy he found a diastase content of 10-33 units, the figure usually given for non-pregnant urines. In eclampsia and the pre-eclamptic state he found the diastase content abnormally high, sometimes reaching 200 units, a figure which, with the exception of certain pancreatic disorders, is not met with in any other conditions. In pyelitis and nephritis a low diastatic excretion is present and he therefore believes the test to be of value in differentiating true pregnancy toxaemia from nephritis complicating pregnancy. He asserts further that the high diastase values in eclampsia indicate that there is little impairment of renal functional efficiency in this condition,/

* The measurement of the diastatic activity of the body fluids, especially of the urine, has been applied to clinical purposes for about ten years. It was originally introduced by Wohlegemuth as a means of diagnosis in pancreatic disease; later it was shewn that whereas in pancreatitis the urinary diastase tended to be increased above normal, conversely in the presence of renal lesions the excretion of diastase in the urine was usually diminished.

condition, a view corroborated by Farr and Williams who failed to demonstrate impairment of kidney function in eclampsia by the phenol-sulphonephthalein test.

Methods of estimating the functional activity of the liver are unsatisfactory and little progress has been made in this direction in the study of the toxaemias of the later months of pregnancy. Reduced urea output has been regarded as evidence of failure of the urea-forming mechanism of the liver. The work of Folin and Denis suggests however that there is an efficient extra hepatic urea forming mechanism. The extraordinary persistence of urea-forming function of the surviving liver in spite of the action of such poisons as phosphorus is illustrated by the recent work of Löffler, and Van Slyke found in a case of acute yellow atrophy that despite almost complete destruction of liver parenchyma a large proportion of urea was still formed. Losee and Van Slyke were unable to demonstrate any rise in the amino-nitrogen of the blood or urine in eclampsia as compared with normal pregnancy and conclude that there is no evidence of impairment of desaminating function in the liver. (de Wesselow)

No evidence of deranged carbohydrate metabolism through impairment of liver function is afforded by

blood/

blood-sugar estimations. These have been carried out by Slemons, Losee, and Mackenzie Wallis, all of whom find normal values. In passing, Wallis draws the interesting deduction that this negatives the hypothesis that the toxaemias of pregnancy are associated with abnormal activity of the endocrine glands, disturbance of function of these glands being almost invariably reflected in an altered blood sugar content.

Recent work shews that the marked accumulation of urea and other nitrogenous waste products, so frequently seen in acute and certain types of chronic nephritis, is absent in eclampsia and allied conditions. The non-protein nitrogen and the blood urea are frequently within normal limits. Absence of definite nitrogen retention is indeed one of the most characteristic features of the disease and serves to differentiate eclampsia from cases of uraemia due to chronic interstitial nephritis complicating pregnancy (Wallis). Fourteen years ago Holland reviewing the literature wrote "the outstanding feature of eclampsia is an auto-intoxication of the body by the toxic products of protein disintegration". More recent biochemical research has cast doubt on the correctness of this view and Slemons (1918) in the light of recent work states "The results of blood analysis give no indication of a derangement of protein metabolism; the evidence/

evidence not only fails to support the protein metabolism hypothesis but even favours its abandonment."

3. The rôle of alimentation in eclampsia.

Although laboratory research appears to demand modification of the metabolic auto-intoxication theory, reference must be made to certain clinical facts which seem to support it. In opening his presidential address before the Obstetrical section of the Royal Acedemy of Medicine, Ireland said: "the cause of eclampsia is no longer a mystery" and proceeded to state that "during pregnancy ordinary food becomes poisonous and may produce eclampsia".

The Dublin method of treatment which, compared with statistics from other centres, yields such good results is based on Tweedy's hypothesis. The effect of a diet poor in proteid was seen in the lowered incidence of eclampsia during the latter years of the war. In an analysis of cases of eclampsia occurring in the Edinburgh Royal Maternity Hospital during the years 1912-1921, the writer found a marked decrease in the years 1916-1918. Bela Varo of the University of Buda Pesth working on a considerable material reported a marked fall in the number of cases of eclampsia during the war years. This fall was more marked in Germany than in Austria, a fact which the writer correlates with the more marked under development/

development of the German population. In Hungary he found that the percentage incidence and mortality remained unaltered during the war among the classes who were able to maintain their standard of living. The maternal mortality fell from 24 per cent before the war to 14 per cent during the war years (de Wesselow). Gessuer noted a steady fall in the Baden statistics of eclampsia from 1913-1918. His figures which are representative of many continental clinics may be quoted.

	Births.	Cases of Eclampsia.	Incidence.
1913	60901	119	0.19
1914	60621	103	0.17
1915	45643	58	0.13
1916	32358	42	0.13
1917	29779	24	0.08

Warnekros refers to an article by Mayer on the marked falling off of eclampsia at the Tübingen clinic and quotes a similar state of affairs at Berlin. In addition to the importance of war diet as a factor he makes the extraordinary suggestion that the disease in question may have been aggravated by "supersaturation of the female organism with the male fertilising principle, a factor largely eliminated by protracted absence of the men at the front"! Bumm has noted

that/

that strong heavily built women are more likely to suffer from the disease than the opposite type and ascribes the higher incidence and more severe form of the disease in northern latitudes to the extra consumption of meat and fat. In spite of biochemical observations these clinical facts strongly suggest that the dietetic factor is of the first importance, if not in the aetiology of the pre-eclamptic state, certainly in its aggravation and in the development of eclampsia.

An attempt has been made in the preceding pages to outline recent advances which seem to throw light on the disordered metabolism which accompanies eclampsia. Our knowledge is as yet insufficient to allow of definite conclusions being drawn; the metabolic factor, however, does not in eclampsia appear to possess the significance which must be assigned to it in the pernicious vomiting of the earlier months.

Linked up with the theory of metabolic poisoning are certain other theories and miscellaneous observations which can be reviewed more conveniently in a later section.

II. THE BACTERIAL THEORY.

The occasional sudden onset, the occurrence of cases in groups, and certain other considerations made it inevitable that a bacterial theory should be propounded. Déloir and Rodet of Lyons in 1884 were the first to suggest bacterial invasion as the responsible factor. Doléris in 1885 and, following him, a large number of observers claimed to have cultivated various organisms from the blood, urine and tissues of eclamptic patients, but their results were so contradictory as to be of little value (W. Williams). On the other hand Haegeler (1892), Döderlein (1893), Schmorl (1893), Lubarsch (1896), Bar and Guyeisse (1897) and Whitridge Williams obtained uniformly negative results. As a consequence of these observations the bacterial hypothesis fell into disfavour, and in a critical review on the etiology of eclampsia published by Holland in 1909, among the numerous theories of origin discussed organismal infection is not mentioned. More recently, probably because of the introduction of improved methods of investigation, a number of papers have appeared in which positive findings have been claimed. It must be admitted however that the results/

results on the whole are not convincing. Speaking generally the arguments advanced in favour of the theory are: 1. The marked genus epidemicus. 2. Its prevalence in populous centres. 3. The accompanying fever. 4. The relative immunity conferred by one attack. 5. Its occasional resemblance to an acute infection, occurring explosively or after a prodrome. 6. The accompanying leucocytosis.*

In only one communication had a definite organism been particularised. C.F. Dick and G.R. Dick (1915) investigating the urine from a case of eclampsia were able to cultivate many slowly growing pin-point transparent colonies consisting of Gram-negative bacilli about the size of the influenza bacillus. Intravenous injection of the organisms, however, produced no apparent effects in dogs, and obviously a communication based on the investigation of a single case/

* Although it is germane to the present subject, the leucocytosis of eclampsia is of sufficient interest to deserve a passing notice. Whereas a white blood count of 10-12,000 is normally found in the later months of pregnancy, with a further increase during labour, in eclampsia the leucocytosis is much greater than in normal pregnancy. Dienst found an average of 26,000 before labour and 40,000 immediately after labour; a similar increase was noted in the albuminuria of pregnancy. He considered the leucocytosis a factor of supreme importance in eclampsia, and looked on the disintegration of leucocytes as the origin of fibrinogen which he regarded as the direct cause of the disease and accountable for all the lesions of eclampsia; he, therefore, advised the employment of hirudin (to inhibit coagulation) in the treatment of Eclampsia.

case has no value.

More recently Talbot (1919) has contributed his views in a lengthy article based on a study of a series of 97 consecutive cases of eclampsia in which from purely clinical as distinct from laboratory observations he has come to the conclusion that in all cases a septic focus of origin may be found if searched for. In all 97 cases, without exception, he found evidence of chronic sepsis in the teeth or gums, and believes that the poisons of a chronic infection in being filtered from the blood stream by the kidneys, damage their excreting mechanism and cause a reduction in their reserve power. He bases his argument on the assumption that the symptoms of eclampsia and the pre-eclamptic state are caused by a retention of the normal physiological waste products of the developing pregnancy, this retention being due to the damaged functional efficiency of the kidneys; and further argues that the increased incidence of the disease in those individuals who have a pre-existing chronic nephritis proves the intimate relation between the occurrence of symptoms and the damaged excretory function of the kidneys, instancing the similarity of symptoms of eclampsia to those of chronic kidney disease as suggestive of a common cause.

Without questioning the accuracy of Talbot's clinical/

clinical observations as regards the presence of a septic focus in all his cases, a high incidence of eclampsia, as distinct from uraemia, in individuals suffering from chronic kidney disease is a point on which all obstetricians are by no means in agreement. Further, as has been indicated above, metabolic intoxication, on which his hypothesis essentially rests, does not appear to play more than a subsidiary rôle from an aetiological standpoint; nor, in the light of the work of Wallis, Slemons, Lisle Williams and others are we warranted in believing that in eclampsia and the pre-eclamptic state the efficiency of the kidney is markedly impaired; the observers mentioned, making use of modern tests of kidney function, are agreed on this point.

Without adducing laboratory evidence in support of his view La Vake (1916) has also expressed himself convinced of a bacterial origin of eclampsia and has described thirteen cases of pre-eclamptic toxaemia in all of which a history or evidence of infection, acute or chronic, could be elicited.

As far as one can judge, no satisfactory evidence has as yet been brought forward in support of a bacterial origin of eclampsia, and until observations are available which are much more elaborate and reliable than any which have so far been recorded, one can only speculate as to a possible rôle played by organismal infection, (see page 105).

III. THE ENDOCRINE SYSTEM AND ECLAMPSIA.

It may seem premature to broach the question of anomalies of endocrine function during gestation when the nature of that function under physiological conditions remains a secret, but in view of the increasing importance being attached to the interaction of the internal secretions, one feels warranted in placing on record the views which have from time to time been advanced concerning the part played by the various ductless glands in relation to eclampsia and the pre-eclamptic state.

1. Thyroid: Lange in 1899 was the first to draw attention to the enlargement of the thyroid gland which so frequently accompanies normal pregnancy and to suggest that in its absence the albuminurias of pregnancy were of more frequent occurrence. Out of 133 pregnant women Lange found thyroid enlargement in 108, and attributed this to a compensatory hypertrophy to meet the demand for increased thyroid secretion as the result of increased metabolism. Of the 108 who shewed thyroid hypertrophy only 2 had albuminuria and in these there was a history of renal disease prior to pregnancy. Of the remaining 22, 16 had albuminuria and tube casts, which/

which in six instances terminated in eclampsia. Lange removed four-fifths of the thyroid gland in eleven cats, six of whom were pregnant and 5 non-pregnant; of the former, five died, three of them with convulsions, and in all albuminuria, and post-mortem, characteristic kidney and liver lesions were noted. Of great interest also are those cases reported by Pineles, Erdheim, and Thaler in which a thyroid-ectomised animal apparently recovered completely from the operation and, becoming pregnant weeks or months afterwards, developed symptoms suggestive of eclampsia, with oliguria, albuminuria, and sometimes convulsions. Lange's observations formed the basis of a clinical investigation by Oliphant Nicholson who emphasized the antagonistic relationship between the internal secretion of the thyroid and that of the suprarenal, especially in regard to their action on the blood-vessels and their influence upon the metabolic processes. He believed that whereas thyroid extract powerfully stimulated both metabolism and elimination, increasing the secretion of urine and excretion of urea, suprarenal extract lowered the general metabolism and might lead to partial or complete suppression of urinary secretion. Nicholson suggested that where the normal physiological thyroid hypertrophy failed to develop, suprarenal overactivity was/

was allowed and was responsible for the high blood-pressure, oliguria, and other phenomena of eclampsia through producing a spasmodic contraction of the arterioles of the body generally and in particular of those of the kidney; on this assumption he claimed good results by re-establishing diuresis by means of thyroid extract.

Fenhinsholz and Parisot (1921) have reported a series of animal experiments in which the influence of the thyroid gland on gestation, parturition and the post-partum state were studied by removing as much of the gland as possible without destroying life or preventing fecundation. Their results were uniform and appeared to show that the pregnant animal was much less able to stand the operation than the non-pregnant; where pregnancy followed extirpation, albuminuria and convulsions were frequent, and where death occurred, suggestive changes in the kidney and liver were commonly found. Such phenomena did not follow extirpation in non-pregnant animals. In 1922,in a further communication,Fenhinsholz reported four cases of pregnancy in women with typical abortive myxoedema; he was impressed by the constancy of renal disturbances in these cases; eclampsia in the first, albuminuria in the second, eclampsia in the third, and oedema in the fourth. Although the numbers quoted are small

these/

these observations lend support to Nicholson's suggestions. The effect of myxoedema on pregnancy is variable. Kocher, to whom one looks for guidance in all questions related to the thyroid, affirms that as a rule pregnancy aggravates the symptoms of myxoedema or reveals them when they are latent. On the other hand, Adam, Walter Wetz, Siredey, Ley, and others have reported cases in which the condition was either unaffected or even improved by the pregnancy. The conclusions which suggest themselves from a survey of the literature are that a physiological enlargement is common during pregnancy, especially in the later months; that where pregnancy occurs in a myxoedematous woman, the symptoms may be relieved or aggravated according to the response which the gland is able to make to the demand for increased secretion. When symptoms do appear, they are those of albuminuria and the pre-eclamptic state. In the majority of cases of thyroid inadequacy however, pregnancy is apparently able to develop along normal lines, so that in the meantime it is difficult completely to correlate the results of animal experiments with that of clinical experience.

Hunter from a review of McCarrison's work agrees that thyroid insufficiency is frequently met with in eclampsia and suggests that the function of this gland is/

is disturbed by bacterial toxins having their origin in the alimentary canal. One effect of this, he believes, is to interfere with the production of that thyroid hormone on which depends the efficiency of the selective or barrier function of the choroid plexus, the result being that endogenous products of metabolism are permitted to enter the cerebro-spinal fluid, producing irritation and convulsions. This view presupposes that in eclampsia the toxic agent is to be found in the cerebro-spinal fluid, which has not yet been proved.*

2. Parathyroid. It was asserted some years ago by Italian investigators that there was an analogy between the tetany following the removal of the parathyroids and eclampsia, and the extract of these glands was recommended for the treatment of the disease. They were able to demonstrate that if hypoparathyroidism is produced in dogs/

* The only reference I can find to the histological changes found in the thyroid gland in eclampsia is in a communication of Pottet and Kervilly (quoted by Holland). These observers examined the gland in four fatal cases. In three they found somewhat complex changes, the chief of which were the presence of many young embryonic vesicles, cirrhosis of the connective tissue, and increased fluidity of the colloid substance. In one case the gland was of normal histological structure. Changes similar to the above were found in three fatal cases of puerperal sepsis.

dogs by partial removal of the glands, the animals, if fed on bread and milk, show no tetanic tendency, but if given meat convulsions develop. From this it was argued that the parathyroids either themselves were active in reducing products of metabolism to excretable substances, or that they activated the liver in this function; and further, that failure to reduce these substances evidenced either a deficient activity of the parathyroids, or that an excessive task was thrown upon them resulting in their break down and failure to function.

Thaler and Adler making use of rats also removed the parathyroids from a large number of animals and noted the appearance of tetany exclusively among the pregnant females, the others being unaffected.

3. Pituitary. In a communication entitled "eclampsia: evolution as a causative factor" S.E. Kark has propounded an ingenious theory that aberration of pituitary function is responsible for the disease. He believes that the early prodromal symptoms are due solely to the overactivity of the anterior lobe, on the hormone of which the physiological requirements of pregnancy normally depend, and emphasizes the resemblance between these prodromal symptoms and acromegaly. Pre-eclamptic symptoms, he suggests, are due to hypertrophy of both parts/

parts of the gland, the increase in size of the gland, through pressure on the optic chiasma, being responsible for the visual symptoms. The phenomena of eclampsia itself, which usually coincide with the onset of labour, result from overactivity of the posterior lobe, which normally is brought into play at this time. The convulsions are due to its pressor action resulting in spasm of the cerebral blood-vessels; a similar explanation for the high blood-pressure is adduced. Kark attempts to explain the post-mortem appearances in the various organs as the result of a generalised arterial spasm having its origin in overactivity of the posterior lobe of the pituitary. He concludes "eclampsia is essentially a physiological process overdone, due to an excess rather than a perversion of an essential product. Why nature should, in the process of gestation overshoot her mark and thus defeat her own aim is due to the comparatively short evolutionary experience she has had of this her newest experiment in reproduction - the placental form." The high blood pressure which so frequently accompanies the kidney of pregnancy (occurring as a rule at a period of pregnancy when according to Kark theory the anterior lobe is active and the posterior passive), the fact that labour commonly does not coincide with the onset of convulsions, that symptoms resembling/

resembling those of eclampsia and the pre-eclamptic state never follow the therapeutic administration of pituitary extract in large doses and over long periods, for example in the treatment of certain types of menorrhagia, and the fact that extract of the posterior lobe of the pituitary has a distinctly stimulating effect on the renal secretory cells inducing diuresis in contrast to the oliguria of eclampsia, are a few of the many flaws which make Kark's theory untenable.

4. Corpus Lutem. In the search for the fons et origo of eclampsia the corpus luteum has not escaped calumny. In 1907 Lambert and Busquet and in 1911 Champy and Gley injected corpus luteum extract into animals and produced paralyses and convulsions. Later, Devraigne and Chirié reproduced their experiments and concluded that the effects produced were of the nature of anaphylaxis. Westermark in 1919 advanced anew the theory that in the corpus luteum was to be found the primary source of the eclamptic poison. He had been impressed with the relative frequency with which toxic symptoms accompanied hydatid mole (which is associated with exaggerated lutein activity) and with the severity of eclampsia when it developed in these cases. He conducted a series of experiments in which corpus luteum extract was injected into animals and found/

found that in non-pregnant animals, while repeated injections usually proved fatal, the post-mortem appearances were neither constant nor suggestive of eclamptic lesions. In pregnant animals, however, he claims that the microscopic findings were in every respect similar to those of eclampsia. In all, eighteen experiments were carried out, the injections were intravenous, and consisted of 3 cc. of fresh corpus luteum suspended in four times its volume of physiological saline. The injections were repeated at intervals of 3 - 5 days and four injections were usually sufficient to cause death. Westermark's results, in that the injections were made intravenously are open to question, for, as Weichardt, Pilz and others have shown, intravenous injections may prove fatal not as the result of toxic action, but merely consequent on the introduction of free cellular elements into the circulation.

Experiments of a similar nature have recently been carried out by Mackenzie Wallis and Everard Williams. These workers used clear protein-free solutions of corpus luteum obtained from freshly killed pigs and from human ovary removed by operation. They report a series of eight experiments in which injections were followed by definitely toxic results, and produced lesions which they claim to be identical with/

with those found in patients dying of eclampsia. They attribute special significance to the occurrence of hypercholesteraemia during pregnancy, especially as this increase occurs about the fourth month of gestation, at a time when the corpus luteum is most active. Injections of corpus luteum increase the cholesterol content of the blood. Further, in eclampsia, much higher figures are found for cholesterol than during normal pregnancy. Mackenzie Wallis and Williams believe that the excess of cholesterol represents an attempt on the part of the body to neutralise the toxic substances elaborated by the corpus luteum.

M.L. Bory (1918) attributes to the corpus luteum a different function in its relation to eclampsia. He is convinced of the correctness of the theory advanced by Fieux and Mauriac, who claimed to have demonstrated the presence of specific toxic bodies elaborated by the placenta and of equally specific antibodies in the blood of pregnant women. Bory is impressed by the coincident and parallel development of the corpus luteum and of these antibodies which are found in greatest concentration in the second and third months of pregnancy, and attributes to the corpus luteum the function of maintaining the equilibrium between these antibodies and the toxins they are/

are called forth to suppress. His view, therefore, differs essentially from that of Wallis and Williams in that he believes that luteal inadequacy, through failure to preserve this equilibrium,may result in eclampsia. Our knowledge of the physiology of the corpus luteum is as yet too scanty to admit of scientific criticism of the views outlined above as to the rôle this organ may play in eclampsia. While experimental investigation suggests that the corpus luteum does contain a toxic substance which in moderately large doses causes death in animals, the theory that toxaemia developing in the late stages of pregnancy, when the corpus luteum has almost completely disappeared, should be caused by over-activity of that gland appears improbable.

IV. A MECHANICAL EXPLANATION OF THE ORIGIN OF ECLAMPSIA.

Before proceeding to discuss the relationship of anaphylaxis to eclampsia, which serves as an introduction to the consideration of the placental theory, mention may be made of a view advanced by Paramore of Rugby who has attempted to explain the phenomena of eclampsia along mechanical lines. Paramore's conception is that the lesions in the maternal viscera precede and give rise to the toxaemia; he regards the toxaemia which ends in eclampsia simply as an aberration of normal metabolism and eclampsia simply a uraemia, distinguishable from other acute uraemias only in its method of production. Given the maternal kidney and liver lesions it is unnecessary to look for a strange toxin arising from elsewhere, and everything in eclampsia except those lesions is, he claims, explained.* Paramore suggests that the kidney and liver necrosis is ischaemic in nature, due to a shutting off of the blood supply, determined by an occlusion of the capillaries, this occlusion being produced/

* Other workers have believed that the maternal visceral lesions were primary. Lever in 1843 believed that puerperal convulsions resulted from undue pressure of the pregnant uterus on the renal veins causing interference with the function of the kidney.

produced not by thrombosis but by pressure. The thrombosis is secondary, not primary, to the necrosis. The pressure is an exaggerated intra-abdominal pressure produced in certain cases of pregnancy, to which rises in pressure induced by activity and especially by labour are superadded. During the performance of a Caesarean section for eclampsia, with a manometer in position, Paramore made the following readings of rectal pressure. Before opening the abdomen the pressure was 35 mm. Hg. (in the normal non-pregnant it is 10 mm. Hg.). On opening the abdomen the abdominal pressure dropped to 30 mm., and after removal of the child to 10 mm. In a series of pregnant women in whom the intra-abdominal pressure was gauged by means of a manometer and pressure bulb in the rectum, two were suffering from eclamptic toxaemia and in these two the highest pressures were found.
As arguments supporting his theory Paramore instances the high incidence of eclampsia in primigravidae, in the unmarried because of tight-lacing, in multiple pregnancy, in hydraminos, in concealed accidental haemorrhage, in all of which the intra-abdominal pressure is unduly high, and finally in strong muscular women, and asks "are we to suppose that the strong muscular type are specially prone to develop strange toxins from placenta, intestine, thyroid, or breast while/

while the weak and diseased react otherwise? Moreover if the disease is due to failure of chemical adaptation, it should occur in the early rather than in the later months of pregnancy. The real explanation is to be found in interference with visceral metabolism caused by the pressure changes incident to pregnancy." Two obvious fallacies in the way of acceptance of this attractive theory are:- first, that eclampsia occasionally does occur at the sixth or seventh month of pregnancy when the intra-abdominal pressure must be less than is common at full term; and second, that with rapidly growing abdominal tumours or with rapidly developing ascites the intra-abdominal tension may be as high as at the full term of pregnancy without the production of any symptoms suggestive of eclampsia. Without embarking at this stage of my thesis on any exposition of the placenta theory, Paramore's findings with regard to increased intra-abdominal pressure have this significance that such a factor may predispose to venous stasis and consequently to placental degeneration. (see p. 106)

V. THE RELATION OF ANAPHYLAXIS TO PREGNANCY AND ECLAMPSIA.

While the suggestion that eclampsia is of the nature of an anaphylactic phenomenon has been practically discarded, in view of their bearing on some aspects of the placental theory, it is proposed to outline in brief the principles which underlay this hypothesis. By anaphylaxis is understood the serious and frequently fatal attack, mainly convulsive, which follows the second inoculation, under specific conditions of time and quality, of certain complex albuminous substances, not of themselves toxic when administered in the same quantity as a single dose (Leith Murray). Although anaphylaxis is not always associated with convulsions, it was perhaps inevitable that the convulsive nature of eclampsia should direct attention to the possibility of its being of this nature. The first suggestion that eclampsia was anaphylactic in character was given by Anderson and Rosenau to whom it occurred that the blood or some protein substances in solution from the foetus or placenta might first sensitise the mother and a subsequent introduction into the system of the mother of a similar substance explain the convulsions.

In/

In their experimental investigations, pregnant and non-pregnant guinea-pigs received a first and, after an appropriate interval, a second injection of guinea-pig foetal blood. Their results were invariably negative. When placenta which had been allowed to autolyse for three hours at 37.0°C. was used, anaphylaxis was readily induced. Leith Murray's experiments (1910) seemed to prove that it was the autolytic rather than the purely placental element which produced the anaphylaxis. Three guinea-pigs received intraperitoneally ½ cc., 1 cc., and 2 cc. respectively of a fresh emulsion of guinea-pig liver, and three weeks later 10 cc. of a fresh emulsion of guinea-pig liver, without obvious result. On the other hand two guinea-pigs receiving at the same interval of time the same amounts of liver which had been allowed to autolyse for 24 hours in an incubator at 37.0°C. shewed undoubted anaphylaxis. Theis (1910), Lockeman (1911), and Gräfenburgh (1911) experimented on the injection of foetal serum into pregnant and non-pregnant animals, and came to the conclusion that the mother was sensitised during pregnancy by small quantities of foetal protein, and that the sudden introduction into her circulation of a quantity of foetal blood would produce an anaphylactic reaction. They claimed that the liver and kidneys, in cases where death followed, presented/

presented lesions characteristic of eclampsia. Eisenrich (1914) on the other hand, as the results of previous investigations had been inconclusive, attempted to decide the question by the passive transmission of hypersensitisation. He sensitised guinea-pigs by the intra-peritoneal injection of maternal serum; after 24-36 hours he gave an intravenous injection of foetal serum. Of fifty guinea-pigs treated in this way, forty-one shewed no symptoms, the remaining nine shewed non-characteristic "pseudo-anaphylactic" symptoms. Sixteen guinea-pigs that had been treated with the serum of eclamptic mothers and children shewed the same symptoms as these last. No animal died of shock.

The most recent paper on the subject is that of Zweifel (1921) who has repeated the experiments of Gräfenburg, Lockeman, and Theiss, but with absolutely negative results. Working with guinea-pigs and rabbits he found that foetal serum, and serum from the placental blood did not sensitise the animals of the same species. He gives reasons for not regarding eclampsia as an anaphylactic phenomenon, such as its non-occurrence in guinea-pigs, and the unfavourable conditions for its production in pregnancy where the mother is constantly exposed to foetal protein and should rather pass into an anti-anaphylactic state.

Although/

Although neither clinically nor in post-mortem appearances is there other than a superficial resemblance between the two conditions, the evidence seems to be clear that an animal can be sensitised by an injection of placenta from its own species. In other words, placenta of a species on injection into a member of that species acts exactly like horse serum in the guinea-pig experiment. Placenta alone seems to have this property, for example liver extract under the same conditions will not do so. There is apparently some factor in the placenta of any species which is alien to the blood of that species. Murray claims to have proved that pregnant animals are already sensitised to placenta, i.e. whereas in a non-pregnant animal two doses of placental extract are necessary to produce anaphylaxis, in a pregnant animal a single dose (corresponding to the second injection of horse-serum in the guinea-pig) will suffice, and deduces that the animal is actively protecting itself from something injurious in its own placenta, (a suggestion, the significance of which will appear when the placental theory of eclampsia is reviewed). While the conferring of anaphylaxis on such an animal is an interesting confirmation of the fact that the animal was sensitised, Murray agrees that from the dissimilarity of the two conditions/

conditions eclampsia cannot be regarded as an anaphylactic reaction, a view endorsed by the experiments of Eisenrich, Fellander, and R.W. Johnstone.

These observations prepare the way for the consideration of the placental theory which may be said to hold the field to-day.

VI. THE PLACENTAL THEORY OF ECLAMPSIA.*

The fact that eclampsia appears solely during or shortly after pregnancy demands that in its ultimate source the poison must be sought in the placenta or foetus. By the passage of foetal metabolic products into the maternal circulation, the foetus has frequently been held responsible. Fehling (1899) and Dienst (1902) advanced this theory and have had many supporters. The arguments commonly given in favour of this view - that a child born of an eclamptic mother may itself show signs, clinically and post-mortem, of a similar poisoning, and that delivery of the child, or its death in utero, is commonly followed by an abatement of symptoms - are not convincing, and are open to other interpretation. In the presence of a profound maternal toxaemia the wonder is that the child is so frequently born unscathed; intra-uterine death is not always followed by a cessation of convulsions; moreover when the child dies the placenta commonly becomes detached from the uterine wall, so that the phenomenon gives equal support to the placental/

* For much information with regard to the earlier researches on the placental theory I am indebted to Holland's critical review.

placental theory of origin; the same explanation obviously applies to the beneficial effects of delivery. The most recent advocate of this (the "foetal") hypothesis is Bory (1918) who reviews in a critical manner the theories from time to time advanced in favour of a placental origin. In particular he deals with the specific reaction in the maternal tissues which may be elicited by an injection of placental extract. This reaction, which will be dealt with more fully in its appropriate place, is more marked, as shewn by the researches of Fieux and Mauriac, in the earlier months of pregnancy and in the later months is usually absent; Bory therefore concludes that exaggerated syncytial activity in any of its forms (Veit, Weichardt, Pilz, Shenk etc.) whether or not it may account for the "toxaemias" of the earlier months cannot possess aetiological importance as regards eclampsia. The fact that no reaction can be obtained in the later months and that in eclampsia, premature senility in the form of infarcts is so often found, suggested to him the idea that eclampsia resulted from placental insufficiency, in that it failed to deal with noxious foetal waste products and allowed the maternal organism to be flooded by them. "L'éclampsie est au placenta ce que l'urémie est au vein, l'ictère grave à la gland hepatique." The strongest argument against the theory/

theory is of course the occurrence of eclampsia in hydatid mole of which numerous cases have been recorded; and as Holland points out, when one considers that eclampsia usually occurs in primigravidae and in young women and vesicular mole in multiparae and older women, eclampsia in the later months, and vesicular mole in the earlier months, it follows that the incidence of eclampsia associated with hydatid mole is relatively great. Whitridge Williams, however, denies that this contention is well founded, as it is quite conceivable that the metabolic processes incident to the continued growth of the chorionic villi may be practically identical with those of the normal foetus.

When Ehrlich propounded his side-chain theory of immunity, this conception was eagerly seized by Veit and his school and upon it they based an elaborate structure, founded upon numerous clinical and experimental investigations.* Veit (1901) believed that during/

* Schmorl was the first to point out that in eclampsia, the presence of the placental cells in the vessels of the lung was a constant feature. He at first affirmed that they were a feature peculiar to eclampsia and were never found otherwise. Later, however, his views were modified; out of 150 cases of pregnancy in which they were present, only 83 were eclamptics, so that they were relatively common in women dying from causes other than eclampsia. They were markedly abundant in two cases of abortion at the 2nd month who died of sepsis. It is now known that this "Zottendeportation" is commonly found in pregnancy both normal and abnormal, but it was Schmorl's discovery which really gave Veit the initial idea of formulating his "placental theory" of eclampsia.

during pregnancy minute portions of placental villi were constantly "deported" into the maternal blood stream and were there dissolved by the blood fluids of the mother. The hypothetical solvent he called a lysin, or more specifically a syncytiolysin. Under normal conditions this sequence was physiological, but where an undue quantity of villous fragments was deported into the maternal blood stream, the syncytiolysins being insufficient to deal with them, they acted on the maternal organism as an unneutralised toxin, producing according to the degree of excess of placental cells over syncytiolysin, varying degrees of toxaemia. In support of his view Veit and Sholten (1902) found that serum drawn from rabbits into whose peritoneal cavity had been introduced pieces of fresh human placenta deprived as far as possible of all foetal and maternal blood agglutinated and partially dissolved a suspension of human placental cells.

Ascoli (1902) and Weichardt (1902) working on the same general principles as those of Veit offered different interpretations. Ascoli prepared artificial syncytiolysins which on injection into animals produced marked nervous phenomena, and concluded that eclampsia resulted not from an excess of circulating placenta cells but from over-production of the lytic substances evoked to dissolve them. It is of significance however, that it was only when the serum was injected/

injected subdurally that any effect comparable to eclampsia was produced, intravenous and subcutaneous injections being innocuous. Weichardt on the other hand explained the mechanism as similar to that found in certain bacterial diseases. He agreed that syncytiolysins were formed both experimentally and in pregnancy, and that placental elements circulating in the blood were destroyed by them, but suggested that eclampsia was caused by endotoxins liberated by the cytolysis of placenta cells. These toxins he termed syncytiotoxins.

Weichardt's account of his experiments and results is the reverse of convincing,and Wormser (1904), Pollak (1904), and Liepmann (1902) who repeated them, obtained uniformly negative results. In Liepmann's experiments cotyledons were aseptically removed from the placenta and placed in a sterile bowl with sterile salt solution. The pieces were then passed through a sterile mincing-machine and finally filtered through a fine sieve. The resulting emulsion was washed repeatedly in sterile salt solution until all blood had as far as possible been removed. The intraperitoneal injection into rabbits of large doses of the emulsion produced albuminuria in two cases only, out of sixteen, its appearance in these two cases being/

being attributed merely to the presence of excess of protein and not regarded as a toxic phenomenon.

On the other hand Liepmann pointed out a new phenomenon. He prepared a specific serum by injecting an emulsion of placental cells into the peritoneal cavity of rabbits and deduced the presence of specific placental antibodies by testing this serum against human placental extract, a precipitin resulting. To meet the objection that the precipitin indicated merely a general human species reaction, in a second series of experiments he removed the precipitate resulting from the addition of human blood serum and then obtained a further precipitate with placental extract (partial precipitation). This specific precipitin reaction, together with the constant presence during pregnancy of placental cells in the mother's circulation suggested to Liepmann that he had discovered a serum test for the diagnosis of pregnancy.

The observations of Kawasoye (1904) seemed to lend further support to the view that the syncytium acted as a toxin within the maternal organism and that it served to induce the production of specific antibodies. This worker placed human placental cells in the serum of pregnant women and obtained a cloudy precipitate and partial dissolution of the cells, a reaction which appeared to indicate the presence of a/

a lysin in the blood of gravid women. The precipitin reaction was negative with the serum of non-pregnant women and of males.

When finally Freund (1907) as the result of a large series of experiments announced that the injection intravenously of placental extract caused the death of rabbits preceded by convulsive seizures and attended with widespread thrombosis, his observations apparently confirming the results of Weichardt and Pilz, the chain of evidence seemed complete. Meanwhile, however, doubting voices were heard, and subsequently the whole course of experimental research was of an adverse nature and appeared to shew that although a definite species reaction undoubtedly existed and could be demonstrated by biological tests, organ or cell specificity (as, for instance, a particular lysin or percipitin for placenta, liver or kidney cells) became more and more problematic.

1. Liepmann's work was adversely criticised by Opitz who attributed Liepmann's failure to obtain positive results with his injections to the repeated washing and mincing of the placenta, a proceeding probably resulting in much loss of syncytium. Opitz removed blood from the placenta by passing salt solution through the umbilical arteries under pressure of one and a half metres of water, the superficial layer/

layer of the decidua was then shaved off and the remaining placenta ground in a mortar with sterile salt solution; a "specific serum" was then prepared by the intraperitoneal injection into animals of this emulsion. He completely failed to obtain a distinctive precipitin on adding serum of pregnant women to this specific serum. He could detect no difference in the reaction given by serum of pregnant women, of eclamptics, of non-pregnant women, of foetuses and of men.

2. Wormser as the result of numerous experiments expressed himself in total disagreement with the results claimed by Veit, Ascoli, Wiechardt, and Liepmann. Wormser carried out two sets of experiments. In the first he prepared the specific serum by injecting placental extract manufactured according to Liepmann's technique; in the second series the placental emulsion was prepared by the method advocated by Opitz. The experiments of Veit, Ascoli, Weichardt and Liepmann were repeated using both types of placental extracts. The results obtained by these observers were criticised as follows.-

(a) Veit's theory. On general grounds untenable; if eclampsia were a direct poisoning by excess of syncytium over synchytiolysin it should be possible to produce it in every pregnant animal by injection of placental cells of a corresponding series; but pregnant/

pregnant animals are not more affected by such an injection than non-pregnant females and males. In addition uniformly negative results were obtained in attempting to produce syncytiolysis in vitro.
(b) Ascoli's theory. If eclampsia were due to an excess of syncytiolysins, the serum of an eclamptic patient should cause cytolysis in vitro of fresh human placental cells; such was not the case. Moreover Ascoli's experiments were valueless, and in repeating them Wormser only obtained one positive result out of six where the injection was subdural, in this case death being due to a direct cerebral injury from the canula. (c) Weichardt's "syncytiotoxin" theory. Repeated fifteen times with uniformly negative results. (d) Liepmann's precipitin reaction. No difference could be detected between the action of specific and normal sera.

3. Pollak (1904) and Aronson (1905) both failed to detect syncytiolysis and precipitation with specific sera, and Pollak repeated Weichardt's experiments with uniformly negative results.

4. An important communication was published in 1907 by R.T. Frank who immunised rabbits against human placental emulsion using three different extracts prepared from placenta; (a) a maceration of human placenta made as bloodless as possible by washing with large/

large quantities of normal saline solution; (b) a maceration of human placenta made blood-free by washing in plain running water; (c) a solution of nucleo-proteid from human placenta.* With these sera all the tests previously employed individually by other investigators were carried out (precipitation, agglutination, haemolysis, cytolysis against placental cells) upon placental extracts, human blood serum, serum obtained from the umbilical cord blood and from retroplacental blood, urine from pregnant women with and without albumen etc. In addition the Bordet-Gengou reaction (complement fixation test) was used for the first time in this connection, because it was regarded as even more delicate than the precipitin reaction. Frank's results constitute a damaging criticism of the observations of Veit and his co-workers, for all the tests shewed that when any positive reaction was obtained, it was a "general human" species reaction, but that not the slightest evidence of a specific placental reaction could be found; he concluded that "he felt justified in making a positive statement that no experimental proof of a specific/

* Placental nucleo-proteid was used because Beebe and Bierry and Pettit had shewn that if the nucleo-proteid prepared from cells, instead of the cells themselves, was injected, a serum was obtained, which was much more sharply specific and gave much less of a "general human" reaction.

specific placental immune reaction could be demonstrated by our present biological methods".

Frank's observations were apparently confirmed by the work of Frankl (1909) and later by Schenk(1910). Frankl's investigations consisted of a series of experiments, in substance identical with those of Frank, and with the same negative outcome. Further, he employed the Wassermann reaction, using the blood serum of patients as amboceptor and placenta as antigen. Schenk also made use of the complement-fixation test with placenta as antigen and failed to find evidence of a specific placental antibody.

The negative results just enumerated almost sufficed to render untenable Veit's hypothesis that eclampsia was due to a specific placental toxin. One other symptom-complex however remained to be accounted for. This was the occurrence of convulsions following intravenous injection of placental extract, such as were obtained by Weichardt and Freund. Weichardt and his supporters believed that the widespread thrombosis found post-mortem resulted from a special toxin elaborated by the placenta. 1. Mathes (1908) criticising Freund's observations was able to shew that the concentration of the extract and the rate of its injection had considerable influence on the production of intravascular coagulation, and while agreeing that placental/

placental extract had toxic properties was able to prevent thrombosis by dilution and slow injection. 2. Englemann and Slade, (1909) however, from a large series of experiments denied that the rate of injection affected the result. They affirmed that the chief effect, and that a toxic one, was a widespread intravascular coagulation; and that death, when it occurred was due to this alone they attempted to demonstrate by introducing along with a fatal dose of placental extract a quantity of hirudin (leech extract) to prevent vascular coagulation; out of fourteen animals thus injected only two died, one from air embolism. 3. Lichtenstein (1909) denied altogether the toxicity of placental extract and offered a different explanation for the occurrence of thrombosis. He obtained an emulsion of placenta by grinding it in a mortar and passing it through a series of sieves of graduated texture; where a very fine sieve was used no result followed, with one less fine widespread intravascular coagulation was the result. Moreover this latter occurrence could be exactly reproduced by the intravenous introduction of inorganic particles (a suspension of fine clay was used). Lichtenstein concluded therefore that death, when it occurred, was produced purely by foreign body effect, through the occurrence of multiple emboli followed by thrombosis, and/

and was in no sense due to toxic properties in the placenta. While the intravascular coagulation which follows intravenous injection of placental extract may be partially attributed to the contained cell debris, it has long been known that nucleo-proteid, prepared from any organ, when injected intravenously is followed by a similar result. That it could be produced by injecting nucleo-proteid prepared from placenta was demonstrated by Accouci (1904) and Dryfuss (1908).

These researches shew that the work of earlier observers and the results obtained by intravenous injection must be regarded in a restricted sense.

Frank's work has already received attention; it may be recalled that as the result of an elaborate research he concluded that no evidence of a specific placental reaction could be obtained. In contract to this must be mentioned the observations of Fieux and Mauriac (1910) who, also making use of the Bordet-Gengou (complement-fixation) reaction, claimed to have demonstrated the presence of specific toxic bodies elaborated by the placenta, and of equally specific antibodies in the blood of pregnant women. These investigators instead of using the serum of pregnant rabbits, immunised against human placenta as the amboceptor, as most other workers had done, employed the/

the blood serum of pregnant women in this rôle, exactly as human serum is used in the Wassermann reaction, and as antigen they used extract prepared from the villi of early ova (taking the place of syphilitic liver in the Wassermann test) instead of full term placenta. Fieux and Mauriac tested the blood serum of fifty-five women, of whom thirty-four were pregnant, the remainder being used as controls. The subjoined table shows the results obtained.

		Results		
Number of cases.	Period of Gestation.	Positive	Negative	Doubtful.
5	3rd-5th week		5	
11	2nd-3rd month	11		
7	3rd-4th "	1	4	2
21	4th-9th "		21	
10	Non-pregnant		10	
54		12	40	2

What impresses one immediately is that positive reactions were obtained only in twelve cases out of fifty-four, all of them during the second and third months of pregnancy, where their association with the fullest development of the trophoblast is obvious. After the third month a negative reaction was uniformly noted. In passing, as far as this individual research/

research is concerned, it seems to negative very definitely the possibility that eclampsia is due either to an excess of syncytial toxin, as Veit and his followers conceived it, or to a deficiency of protection developed.

With the results of Fieux and Mauriac, Frank and Heimann (1911) expressed themselves in complete disagreement. Frank's earlier paper has already been noted, and in view of the results claimed by Fieux and Mauriac, the second research was undertaken to vindicate the observations previously made. Frank and Heimann, therefore, decided to repeat the experiments of Fieux and Mauriac, employing the same technique as had been used by them. In their investigations eighteen sera were examined; of these, nine were obtained from women who were in the second or third month of gestation, the other nine were drawn from patients who were in the later months of pregnancy. Uniformly negative results were obtained with all sera, with the exception of one where the reaction was doubtful. Apart from the suggestion offered by Frank and Heimann that Fieux and Mauriac might unwittingly have performed a true Wassermann reaction for syphilis, in that their antigens might have contained luetic inhibitory substances and their sera luetic antibodies, it is difficult to explain such

a/

a variance in results.

In the light of more recent work it is probable that Frank and Heimann went too far in denying altogether that there is in the placenta some body or antigen which is capable of producing antibodies in the species, i.e. of stimulating the body tissues and fluids to immunise themselves. Murray, whose earlier work in relation to anaphylaxis and eclampsia has already been referred to, was able to adduce convincing evidence that pregnant animals are already sensitised to placenta; whereas in a non-pregnant animal two doses of placental extract were necessary to produce anaphylaxis, in a pregnant animal a single dose (corresponding to the second injection of horse serum in the guinea-pig) would suffice. And, as lending support to Fieux and Mauriac's observations, he found that the anaphylaxis induced in a pregnant animal by a solitary injection of placental extract was much more severe in early pregnancy and might be rapidly fatal in a pregnancy so early as to be microscopic.

Obata of Tokio has recently (1919) published results of a similar investigation. His technique was as follows: (I quote from a recent leading article in the Lancet). As soon as the placenta was expelled the umbilical cord was cut off together with the portion of placenta surrounding its attachment.

As/

As much blood as possible was then expressed from the placenta and the decidual tissue removed. A portion of the remainder of the placenta was then cut in pieces, ground in a mortar and mixed with 0.85% saline solution, in proportion of 1 in 3 by weight. The mixture was stirred and allowed to stand for half-an-hour at room temperature, and then filtered through fine silk. The filtrate was then centrifuged and the supernatant fluid, designated placental extract, was used for the experiments. The extract had a pale pink colour, but contained no solid particles. As a rule freshly prepared extracts from placentae taken immediately after birth were employed. The animals used for injection were Japanese dancing-mice and the placental extract was injected into their caudal vein. In the majority of cases after an interval of 30 - 60 seconds the animal became excited, and convulsions followed by death rapidly developed; occasionally however death occurred after an interval of hours or days. The lesions found in the bodies of animals who succumbed were broadly similar to those present in fatal cases of eclampsia in the human. The placental extract was found to kill in a dose of 0.025 - 1.5 cc. in the case of normal placentae and in a dose of 0.019 - 0.1 cc. in the case of eclamptic placentae. The toxicity of eclamptic placentae, accordingly, was hardly/

hardly to be distinguished from that of placenta from normal cases. Obata then proceeded to determine the relative capacity of fresh serum of normal and of eclamptic patients respectively to neutralise the toxicity of placental extract. 1 cc. of the latter was placed in contact with amounts of serum varying from 0.7 to 0.025 cc., physiological saline being added to bring the mixture up to 2 cc. and the fluid injected after being left for one hour at 37°C. He found that serum either of normal men or of normal non-pregnant or normal pregnant women possessed a power practically uniform of neutralising the poisonous properties of placental extract, 0.2 - 0.3 cc. of such serum sufficing to neutralise 1 cc. of the extract. This neutralising power was found to be considerably reduced in the serum from women during an eclamptic attack, as much as 0.6 cc. being then required to neutralise the toxicity of the placental extract, although after recovering from eclampsia 0.3 - 0.4 cc. and sometimes 0.2 cc. of the patient's serum was sufficient. Experiments made to determine whether the neutralising power was increased during normal pregnancy were negative. Hence no evidence was found to indicate that the neutralising power was due to an immunological process. Obata concluded that eclampsia consisted in an intoxication of the maternal organism by a placental poison which was made possible by/

by the failure of the maternal blood to supply an efficient neutralising principle. It is of interest to note in passing that fresh serum from normal persons when injected intravenously into mice produces symptoms which differ only slightly from those produced by placental extract. No substantial difference moreover was found between the serum of normal and of eclamptic gravidae in this respect, nor could any increase in toxicity be found in the serum of a patient during an attack of eclampsia and after recovery from that condition. Obata's technique is very similar to that first used by Liepmann and adversely criticised by Opitz; his experiments are in nature essentially those carried out by Freund in 1907 and are therefore open to the same criticism (of results following intravenous injections) as were advanced by Mathes, Engelman, Slade and Lichtenstein. In general they lend support to the view that the introduction of placental extract under certain circumstances may result in a reaction more or less specific, but as regards the etiology of eclampsia they do not seem to any appreciable extent to advance our knowledge.

Such then is the placental theory of eclampsia as conceived originally by Veit and elaborated by the numerous investigators who followed him. Sufficient alone to cast grave doubts on its correctness are

the diametrically opposite conclusions arrived at by different observers working along practically the same lines. While it seems clear from the researches of Fieux and Mauriac, of Murray, and of Abderhalden that a specific maternal reaction, of the nature of antibody formation to placenta as antigen may occur, it is equally clear that this is most marked in early pregnancy, completely disappearing during the later months, and that the hypothesis that eclampsia may be due either to an excess of syncytial toxin (as Veit and his followers understood it) or to deficient development of protection against it, is a theory not supported by sufficient evidence to warrant its existence.

To Liepmann belongs the credit of first advancing the view that it is in the <u>eclamptic</u> placenta that one must look for the cause of the disease.*
Hoping to produce a specific antibody for eclampsia analogous to the immunity which Weichardt and Opitz had been able to produce against large doses of normal placentae by the injection of small doses, Liepmann was working with a dry powder, manufactured from eclamptic placentae, which he injected into the peritoneal cavity of rabbits. To his surprise the animals quickly died, with all the symptoms of a severe/

* The following account of Liepmann's work is taken from Holland's Critical Review.

severe intoxication. Control experiments made with normal placentae gave negative results. He drew the conclusion that in the eclamptic placenta existed a poison not present in normal placentae. His technique was as follows:- The placentae of eclamptic patients were minced, dried in vacuo, and ground into a fine white powder. Of this powder a suspension in salt solution was made and a definite dose, usually 1 gm. of powder was injected into the peritoneal cavity of rabbits. Of seventy animals injected only thirteen lived, and these shewed severe disturbances shortly after the injections. As regards the manner in which the toxin exists in the placenta, experiment shewed that it was firmly combined with the protoplasm of the cell. The juices of the eclamptic placenta were separated from the pulp in a Buchner's press. Injection of the placenta pulp proved fatal, whereas the juices of the same placenta, when injected intravenously produced no bad effect. But in placentae from cases of very severe toxaemia a smaller proportion of the toxin was found in the extracted juices as well. Further, it was found that the extract, when toxic, could be deprived of its toxicity on the addition of reagents which precipitate albumen; they either precipitated the toxin or carried it down with the precipitate. That the toxin was very labile and difficult/

difficult to preserve was shewn by trials of the same placenta powder at different dates; the powder which proved fatal on one day was innocuous on the day following. Attempts to extract the toxin by chemical means failed. In further experiments Liepmann found that extracts of placenta from severe cases of eclampsia were less toxic than extracts from milder types, and deduced from this that the greater the amount of toxin that was passed over into the organism and the more the number of fits that occurred, the less was the amount of toxin found in the placenta; conversely, the placenta was so much the richer in toxin the fewer the fits that occurred. Although objection may be taken to Liepmann's work on the ground that his placentae were prepared in a factory on a large scale and therefore must have run the risk of decomposition before the powder was finally ready, he escapes the criticism which may be passed on the results of many other workers in that he obtained positive results by means of intraperitoneal and not intravenous injection; the fallacy attached to this latter method has already been indicated. Further, in directing the search for the source of toxaemia to the eclamptic rather than to the normal placenta he broke new ground.

Many workers have sought to find the source of eclampsia/

eclampsia in a study of the placental ferments, which are exceedingly numerous and complex and are apparently increased in activity in eclampsia. Savaré (1906) claimed to have discovered a ferment which might be responsible through its powerful action in causing intravascular coagulation. Mohr and Freund (1908) were able to extract from the placenta a lipoid with strongly haemolytic properties. Hofbauer (1918) in a series of lengthy articles regards the placenta as the seat of ferments which under certain conditions may become altered and produce autolytic degeneration in the liver. Finally Schönfeld (1921) attributes eclampsia to the perverted activity of a lipoid normally present in the placenta. This substance he was able to isolate and claims by his intravenous introduction to have produced eclampsia in animals.

The foregoing review, while it does not pretend to be completely comprehensive, embraces the bulk of the work on the etiology of eclampsia carried out in recent years with the exception of the research of James Young who seeks to explain the phenomenon as resulting from the liberation of products of early autolysis of the placenta, a theory which I shall endeavour to substantiate. Before Young published his results/

results autolysis of the placenta had received considerable attention from Mathes (1901) Basso (1905) and in particular Dryfuss (1907) who investigated very fully the autolysis of normal and of eclamptic placentae from the chemical standpoint without drawing conclusions as to its rôle in the production of the eclamptic state.

PART II.

PART II.

Before proceeding to a detailed consideration of the infarction theory, with which my thesis is principally concerned, it is expedient to bring under review certain changes which may be met with characteristically in the eclamptic placenta, for, on the significance of these, Young's hypothesis essentially rests. The appearances found may be grouped as follows:-

(1) Haemorrhagic lesions. These have been variously termed; apoplexy (Cruveilhier, Jacquemier, Gierse, Meckeland Williams); haematoma (Klebs); haemorrhage (Kuehnel, Simpson, Brindean and Nattan-Larrier); red infarcts (Williams, Young and others); these last will be considered under the heading infarction.

Brindean and Nattan-Larrier describe three forms of haemorrhage, (a) the haemorrhagic nodule or cyst, (b) diffuse haemorrhage into the substance of the placenta, or placental apoplexy, (c) the retro-placental haematoma; this last type will be considered under ante-partum haemorrhage. The former two varieties are stated by Brindean and Nattan-Larrier to/

to be due to rupture of villous vessels consequent on their overdilatation, in other words the haemorrhage is foetal in origin. McNalley and Dickmann on the other hand, who have also studied these intra-placental haemorrhages, have decided in favour of a maternal origin and have stated that they probably result from back pressure due to venous stasis from thrombosis, the size of the lesion being in proportion to the extent of the interference with the return flow. This explanation was suggested by Young in 1914. Such intraplacental haemorrhages, while very frequent in eclampsia and albuminuria, may of course be met with in other conditions. Their significance is uncertain. In thirty-two eclamptic placentae investigated by myself they were present in eleven cases. The haemorrhagic cyst may, through interference with the maternal blood supply to the underlying portion of the placenta, be subtended by an arc of infarcted tissue. In other cases the tissue surrounding the haematoma may have become solidified merely as the result of pressure.

(2) Epithelial Plates. J.L. Brenner (1918) has called attention to certain thin epithelial plates to be found in the surface layer of the placental villi in intimate connection/

connection with the underlying foetal capillaries, "similar in appearance and relations to the epithelial plates of the visceral layer of the capsule of the renal or mesonephric glomerulus", and has claimed to show that such plates are present in the placenta only during the absence or degeneration of the mesonephros in any particular type of embryo. He suggests that the presence of these plates shows the ability of the placenta to remove from the foetal blood certain excretory substances and to assume for the foetus the function of glomeruli. Normally the plates are scattered and only found after careful search. In eclamptic placentae, Brenner states, their numbers are greatly increased, and their detection correspondingly easier.

(3) Infarction. Placental disease of the nature of infarction has been recognised as a common accompaniment of the toxaemic states in the later months of pregnancy since Fehling first drew attention to the connection in 1886.

Infarction may usefully be considered under the following headings:- /

headings:-

FREQUENCY OF INFARCTION IN ALBUMINURIA AND ECLAMPSIA.

The typical case of long-standing pregnancy albuminuria always shows multiple areas of infarction, varying in age and appearance. Their relative frequency has been variously estimated by different observers. Rouhaud, in 1882, noted that 40 per cent of the cases which had albuminuria had red infarcts. Rossier found infarction in 60 per cent of albuminuric placentae. Mayer stated infarction to be four times more frequent when the patient was albuminuric than when the urine was healthy, (although he only found a percentage of 6.7 albuminuric patients were delivered of infarcted placentae); Cagny found infarction in 33 per cent of placentae obtained from albuminuric patients; Martin in 47 per cent. Williams from whom these figures are quoted found infarction in 63 per cent of a series of five hundred placentae, though he does not state in what proportion of these albuminuria was noted. Haffner (1921) has recently reported the results of an examination of a consecutive series of four hundred placentae, and has investigated the relative incidence of albuminuria and infarction. In seventy-three albuminuric patients infarction was found in 56 per cent; of one hundred and eighty-five placentae showing infarction, 77 per cent were obtained from/

from women in whose urine no albumen was detected; moreover, in 30 per cent of these placentae the infarctions were recent. Haffner concludes accordingly that there is insufficient justification for believing that any direct relationship exists between albuminuria and placental infarction.

In spite of Haffner's adverse criticism the mass of evidence suggests that, however the relationship be explained, infarction and albuminuria are closely associated; with this view my personal observations are in accord. The material employed for this investigation consisted of two hundred and forty-six consecutive delivery cases which were observed from the point of view of albuminuria and the changes met with in the placenta. The two hundred and forty-six patients were classified as follows:-

(1) Cases admitted to the Maternity Hospital immediately preceding or during labour, whose history as regards the condition of the urine during pregnancy was unknown; these numbered one hundred and sixty-seven.

(2) Cases admitted whose previous history as regards the urine was accurately known; there were seventy-nine patients in this category.

The following table shows at a glance in what proportion albumen was present and the incidence of infarction.

	Urine.	Infarction.
1. Cases admitted with no previous record: 167.	albumen absent, 74	12 = 16.2%
	albumen present,93	68 = 73.1%
2. Cases whose previous history was known: 79.	albumen absent 32	63 = 18.7%
	*albumen present 47	34 = 72%

* This includes cases which had albumen present on admission to hospital, or gave a history of albuminuria at some time during the later months of pregnancy.

The one hundred and forty albuminuric patients were further classified as far as possible as follows:-

(1) Cases of "true" albuminuria of pregnancy. These numbered sixty-seven and were restricted to cases presenting definite symptoms of toxaemia. In sixty-two cases (92.5 per cent) infarction was present. One of the remaining five was a case of fulminating eclampsia, coming on with no prodromal symptoms; the placenta was apparently normal; the explanation of this apparent paradox will be suggested later.

(2) Cases of nephritis complicating pregnancy. These numbered four. All had a long history of previous kidney trouble and the condition of the heart and blood vessels suggested chronic Brights' disease. In two the placenta was abnormal.

(3) Cases showing a symptomless albuminuria, more or less transient. These numbered sixty-nine and are of certain interest. In thirty-eight cases (55 per cent) the placenta contained recent infarcts, most of them small, varying in size from a pea to a filbert. This type of symptomless albuminuria, present in 28 per cent of cases in my series of two hundred and forty-six deliveries, is usually looked on as physio-

physiological in nature, the result of the fatigue incident to labour; moreover such infarction as was present in the placentae of these cases is commonly, and without doubt correctly, regarded as a normal occurrence, "a sign of senility in a short-lived organ" (Eden). While fatigue, anaesthesia etc. no doubt do play a part in the production of these transient albuminurias, in the light of Young's work the question obtrudes itself as to whether a direct association may not exist between this so-called physiological albuminuria and the slighter degrees of infarction which may be met with in the average full-term placenta. In other words, is not the trace of albumen sometimes toxic in nature? The question cannot be satisfactorily answered until a more delicate test for the presence of toxaemia than albumen in the urine is available.

THE PATHOLOGY OF INFARCTION.

The material available for this study consisted of a hundred and seventy-nine placentae in which degenerative changes of this nature had occurred. The examination of the placenta consisted in inspection of the maternal surface, after it had been washed/

washed free of blood clot, and in careful palpation of the organ to detect areas of greater resistance; such a superficial examination may be sufficient to make out the larger or older brick-red or yellow infarcted areas. The recent infarction, however, may differ only slightly in consistence and colour from that of the normal fresh placental tissue, and may escape notice. In addition, therefore, as a routine, each placenta was serially sectioned with a long-bladed knife and examined under running water, thus rinsing the inter-villous blood out of the healthy parts of the placenta. The deep red or purple colour of recently infarcted areas (in which the blood is clotted and therefore not removed by washing) was thus thrown into relief against the paler surrounding tissue,and the detection of such areas, which might otherwise have been missed, was simple. This technique was found more satisfactory than the usual formalin method. Further, in the majority of cases, all areas showing anything unusual were submitted to microscopic examination.

The appearances found are for convenience of description recorded here according as the development of infarction was in its early, intermediate, or late stages. The classification is necessarily arbitrary, for, as will be indicated later, the process is a

continuous/

continuous one, one stage gradually merging into the next.

(1) Early. In the earliest stages an area of infarction may differ little in colour from normal placenta, and unless the placenta is sectioned and examined under running water as described above, may escape notice. When treated in this manner, however, the lesion shows up as a very dark red or purple patch, sometimes sharply defined from the adjoining healthy tissue. The infarcted area may be found in some cases accurately to subtend a retro-placental haematoma. At this stage the open spongy texture of the placenta may still be observed and there is little or no change in consistence. (see Plates V & VI). The infarct of a few days standing is somewhat lighter in colour and firmer in consistence; the resemblance to liver in appearance and consistence has led to the term "hepatisation", which accurately describes the character of the lesion at this stage.

Microscopically, (see microphotographs 3 to 9), the earliest change seen consists in a marked congestion of the blood vessels of the chorionic villi. It should be remembered in this connection that the degree of congestion of the villous vessels throughout/

throughout the placenta is naturally influenced by the time at which the cord is tied, being more pronounced when the cord is ligated immediately after birth, than when the ligature is not applied until pulsation has ceased. In the infarcted area the vessels are often so distended as to compress the stroma into a very thin layer under the epithelial covering. The congestion of the villous vessels may be looked on as analogous to the congestion seen in the development of a collateral circulation elsewhere. Young has compared it to "the vascular hyperaemia and stagnation which occurs in other tissues when there is any local lowering in vitality such as might result, for example, from injury. It is an evidence of local reaction, which precedes the local death, that is envitable when the blood supply of the part is cut off". In association with this congestion the villi are commonly found closely crowded together, so that the intervillous spaces are reduced to mere chinks, or are completely obliterated, the result being a solid block of tissue more or less sharply differentiated from the surrounding spongy placental substance.

This "hepatisation" is not entirely due to the turgescence of the individual villi. Eden explained it as due to a "progressive diminution of the blood supply/

supply to a part of a cotyledon by the obliteration of a maternal artery, which would cause the villi to become crowded together because there would not be sufficient blood in the part to maintain them at their normal distance from one another", and suggested further that the pressure exerted by the rest of the placenta "would drive the villi together into a closely crowded consolidated mass". With this explanation Young is in agreement and writes "the infarcted block is thus really an area of collapsed placental tissue ..... comparable to collapse of a portion of the lung following occlusion of a corresponding bronchus".

A third feature of the early infarct is the presence of a coagulum in the intervillous spaces; this, while not a constant, is a characteristic finding, (see case 9, Section (1); and case 10, Section (1)). Clotting of blood in this situation is never found in the healthy placenta. According to Young, its occurrence always indicates interference with the maternal circulation in the corresponding part, and is not necessarily secondary to the changes in the villi; he instances its occurrence in cases where it is known that there has been a stagnation of the maternal blood, and where the villi are healthy, e.g. accidental haemorrhage. Coincident with the appearances above described, degenerative changes may occasionally/

occasionally be found in the chorionic epithelium. The earliest indication of necrosis seems to be a proliferation of the epithelium in the form of projecting buds of granular syncytium staining deeply with haematin. Young, drawing attention to this feature, refers to the masses of tissue as "proliferation of the syncytial nuclei". The condition has been described by various investigators (Fink, Hermann, Sitz, etc.) as characteristic of the albuminuric or eclamptic placenta. Brindean and Nattan-Larrier, however, do not consider this budding peculiar to eclampsia, but merely an exaggeration of the physiological condition.

(2) Intermediate. In this stage the deep purple of the early infarct has given place to a brick-red or reddish-brown; solidification has occurred, the infarct having the consistence of india-rubber and cutting with a smooth surface. The lesion is now so sharply defined from the surrounding healthy tissue that it forms a prominent feature of the cut-section of the placenta.

Microscopically, (see microphotographs 10 to 12), the most noticeable change is the pallor of the blood in the vessels of the villi and in the intervillous spaces as the result of removal of haemoglobin and imperfect absorption of staining matter. Young has pointed/

pointed this out and explains thereby the alteration in the naked eye appearance of the infarct. Epithelial degeneration is further advanced, the nuclei staining feebly or not at all. Degeneration of the stroma, of the nature of a coagulation necrosis, has also occurred. In this stage, fusion of neighbouring villi by masses of fibrin or by adhesion of their epithelial surfaces is commonly found and is sometimes so pronounced that the outlines of individual villi are difficult to distinguish.

(3) Late. In its ultimate stages, its distinctive pale yellow appearance and hard consistence make the naked-eye recognition of infarction easy. Microscopically, (see microphotograph 13), the villi are commonly seen fused into a more or less homogenous mass of tissue, in which epithelial degeneration is complete, nuclear staining being entirely lost. Necrosis of the stroma is pronounced, and little or no trace of foetal vessels remains. Less commonly a different terminal stage may be observed in which no fusion of the villi occurs, but in which disintegration of their cellular elements progresses until in the end they are represented by mere ghost-like outlines, (see microphotograph 14). Young, so far as I know, was the first to point out that the various appearances included under the term "infarction" are/

are different stages in one and the same process, and not, as often stated, independent pathological states. His views are in disagreement with those of Whitridge Williams, but have been endorsed in a recent article by McNalley and Dickman, who, while agreeing that the white infarct ..... generally represents a further or older stage of the red variety, describe a further type of lesion which results from the conversion of a collection of pure blood into structures that, in the gross, have the identical appearance of white infarcts, but in whose formation villi play no part. This condition has also been described by Dieulafoy who writes "The lesion is characterised by the appearance of haemorrhages which are converted into white infarct. The primary lesion is haemorrhagic, the white infarct is secondary. If the infarct is incised it appears to be formed by fibrin, more or less dense in appearance and sometimes disposed in a series of concentric lines". Cruveilhier and De Lee have made similar observations.

AETIOLOGY OF INFARCTION.

The factors responsible for infarction are disputed. Whitridge Williams from an examination of five hundred placentae concluded that in the great majority of/

of cases the main factor in the production of infarction was to be found in an obliterative endarteritis of the villous vessels. His observations were thus in accordance with those already made by Eden, Ackermann and others. Young on the other hand agrees with Hofmeir that the degeneration is due to some interference with the maternal blood supply, and has pointed out that the villi are not dependent for their nourishment on the foetal blood and that they can live and proliferate when this is absent, as in the earliest stages of development, or in hydatid mole, and therefore that villous necrosis must be the result of some process other than obliteration of the villous vessels.

Young's observations receive support from the work of Goodall, who has shewn in his investigation on the involuting uterus, that obliteration of the maternal vessels does take place before labour; "in the smaller veins of the placental area": he writes "there is usually a complete obliteration due to the building of a thrombus". Goodall has pointed further to the connection between these changes and the presence of placental infarcts.

That infarction results from interference with the maternal blood supply is shewn clearly by the frequency with which a retroplacental clot is accurately subtended/

subtended by an area of infarction. Underlying old clots old yellowish or white infarctions will be found, while under a recent haematoma the area of infarction is deep red or purple; such infarction as this last commonly accompanies accidental haemorrhage, especially of the concealed variety, and I have repeatedly found it in the separated portion of a placenta praevia. (see plates IX & X).

In many instances, in fact in the majority of cases of eclampsia, no evidence of placental separation or of retroplacental bleeding may be present, the local impairment of blood supply that results in placental infarction being probably due to thrombosis in the vessels of the placental site. (see pp. 105, 106)

THE AETIOLOGICAL RELATIONSHIPS OF INFARCTION AND THE ALBUMINURIA OF PREGNANCY.

This has been much disputed. Holland, while admitting that infarcts were more frequent in albuminuria and eclampsia, wrote "they may be looked on as the result of a chronic toxaemia; as to their connection with eclampsia, they are merely accompaniments not consequences. The presence of the chronic degenerations in eclamptic placentae has been investigated by Brindeau and Nattan-Larrier who give them no special significance."/

significance." Whitridge Williams, while recognising their association with eclampsia and albuminuria stated that at present we could not satisfactorily account for the relationship between them. More recently Hoffbauer has denied that the two conditions are in any sense associated. Until Young's paper in 1914 one may summarise the position by saying that placental disease of this nature was looked on merely as the accompaniment or as the result of the toxaemic state. This attitude was the natural outcome of the variable and confusing changes which might be found in the placenta in toxaemic cases. In the majority of cases of toxaemia an extensive degree of placental infarction is found; in others there is no apparent change; in a third group the placenta may contain multiple areas of necrosis, and yet, at the time of delivery, no clinical evidence of toxaemia may be present. The natural inference from such irreconcilable data was that no constant association between the two conditions existed. A logical explanation however has been offered by Young. What first led him to the interpretation of this apparent paradox, was the discovery that, although obvious placental disease might be absent in the placenta of a fulminating eclampsia which ended in rapid labour or death, in the other less virulent type, in which some days or weeks/

weeks elapse between the inception of the toxaemia and the birth of the placenta, there is always massive necrosis visible to the naked eye. In my own series of cases I have seen no exception to this rule, and would specially direct the reader's attention to Cases 43 and 44 which are illustrative of this explanation.* The obvious deduction from these observations is that in an albuminuric or eclamptic toxaemia a degenerative change is always present in the placenta, but that some hours or possibly a day must elapse before it can evolve into the form of naked eye infarction. Quoting from Young's 1914 paper (p.4): "It is this that explains why in an albuminuria which becomes established gradually and persists for some time, one is more likely to find marked placental disease. It is just the comparatively slow involvement of the placenta that allows of the continuance of the pregnancy and the evolution of the infarcted regions. Where there is a sudden and extensive involvement of the placenta, the toxaemia is/

* A case similar to No.44 has recently (16th September 1923) been delivered in the Royal Maternity Hospital. The patient, a primigravida, apparently enjoyed perfect health until the onset of labour. Her urine had been tested at frequent intervals in the Antenatal Department with negative results, the last analysis being made eight days before labour. Towards the end of the first stage of labour, the patient became stuperose and complained of violent headache; two eclamptic convulsions occurred before delivery was completed. The placenta was thoroughly sectioned and, as far as one could judge, was in every respect normal.

is so fulminant that the pregnancy ends before any naked-eye changes in the placenta are produced."

If these observations are correct they indicate that if the necrotic areas are the source of the eclamptic poison, this poison is produced during the early autolysis of the disintegration process, and whilst the structure of the placenta as yet shews little or no change. Gradual piecemeal involvement of the placenta may produce in the end an extensive infarction consisting of small isolated necrotic areas of different ages but "under these circumstances the absorption of toxic products from the dying patches is so gradual and at any one time so small in amount that it is tolerated and may occur with little outward effect." (Young).

In that type of case mentioned above, in which, despite the presence of obvious infarction, no toxaemia is evident at the time of delivery, we are dealing with a toxaemia which was present earlier in the course of pregnancy and has been recovered from. In such, the infarction will obviously be other than recent. (see Case 46).

ACCIDENTAL HAEMORRHAGE AND TOXAEMIA.

On account of the frequency with which it is associated with albuminuria and eclampsia, accidental haemorrhage is a subject of great importance in connection with the thesis which I am attempting to establish. As early as 1903 Muus of Copenhagen advanced the hypothesis that accidental haemorrhage was a manifestation of a pregnancy toxaemia, and called attention to the frequent association of eclampsia in these cases. Its relation to eclampsia was referred to in 1914 by Essen Moller who described two cases from his own clinic. Numerous other cases have been reported, in particular by Seitz, Winter, Bar, Convelaire, and Willson. In my own series there are five examples of this combination.

PATHOLOGICAL ANATOMY.

For the study of the anatomical changes in accidental haemorrhage, my material has consisted of three uteri, to one of which the placenta was still attached, and twenty-five placentae. The uteri were obtained from cases of severe concealed accidental haemorrhage; in one case the patient had been delivered by/

by Caesarean section followed by hysterectomy; in a second the uterus had been removed entire at abdominal section without having been incised; the third uterus was secured at a post-mortem. The appearances found, which are described in detail in cases 2, 6, and 16, may be summarised as follows:-

(1) Macroscopic appearance of uterus.

In all three cases the naked-eye appearance of the uterus was similar, and presented the striking picture characteristic of the condition (see Plates I & II). The surface of the organ was extensively congested and haemorrhagic, the colours varying from pink through purple to black. In two cases the extravasation was most marked in the neighbourhood of the fundus, in the third case it extended from fundus to lower uterine segment, being equally pronounced in this latter situation. In general, it was found that the ecchymosis was most marked in the tissues overlying the placental site. Splitting of the peritoneal coat was observed in one case, the fissures running for the most part longitudinally, and being more numerous in the neighbourhood of the fundus than elsewhere. This peritoneal fissuring is of interest and has been frequently described by Lieven, Williams, Willson, Smyly and others. The explanation/

explanation of its production is not clear; the condition has been variously ascribed to sudden severe overdistension of the uterus, or to intramuscular haemorrhage with diminished elasticity of the uterine wall, or to the presence of sub-peritoneal collections of blood; such bullae were found in one of my cases.

(2) Myometrium: Widespread intramuscular haemorrhage was found in all three cases.

Separation and tearing apart of muscular bundles is the essential and most constant feature of concealed accidental haemorrhage, and has been described by all those who have studied the condition, in particular by Convelaire, Fletcher Shaw, Ley, Whitridge Williams and Willson. It varies from milder degrees in which infiltration is slight to major degrees in which the uterine wall is ploughed up and masses of tissue are torn asunder by a massive and brutal haemorrhage, the "diffuse utero-placental apoplexy" of Convelaire. In all three cases the extravasation was most marked in the neighbourhood of the placental site, and, especially in two of the cases, towards the fundus rather than towards the lower uterine segment. As regards the distribution of the haemorrhage in the uterine wall, a striking feature, to which attention has been specially drawn by/

by Willson, is the tendency for the haemorrhage to be most widespread towards the peritoneal rather than towards the decidual surface of the uterus. This finding is clearly demonstrated in Case 16 (see Plate II fig 2) and, as will appear later, is of considerable aetiological importance.

As regards the condition of the muscular fibres themselves, all stages of degeneration were found in each case, being apparent for the most part in loss of nuclear staining. In one case the muscle had been reduced in places to a pulp of vacuolated faintly staining tissue. Degeneration of individual muscle fibres has been observed (quoting from Ley's paper) by Seitz, Hartmann and by Larate, but has not been recorded by Courellaire, Essen-Moller or Whitridge Williams. Ley has found marked necrosis in all three uteri studied, and while this was most marked in areas where haemorrhage was greatest, it was not limited to these, and was due, in his opinion, not to the haemorrhage, but to the action of a toxin which in places had converted the muscular tissue into a "vacuolated matrix in which lie a very few tortuous, narrow, hyper- and hypo- chromatic nuclei".

(3) Decidua: Congestion of, and haemorrhage into the decidua were present in all three cases, and were more marked in the neighbourhood/

neighbourhood of the decidua basalis than elsewhere. Leucocytic infiltration of the decidua was found in one case but was not marked. Haemorrhagic lesions of the decidua are described in practically all the recorded cases.

(4) Blood vessels: Congestion, especially of the veins was uniformly present in the three uteri studied; in one section (case 2 section 1) rupture of a vein with effusion into the surrounding tissues, such as has been described by Williams and Convelarie, was found. Thrombosis of the veins of the uterine wall, especially near the placental site, was noted in one case (case 16); in one case (case 2) the ovarian vein on the left side was found to be plugged by a thrombus, though whether of ante-mortem or post-mortem formation, one could not be sure. In Young's case "a massive, extensive and fairly old standing thrombosis was found in the ovarian vessels on each side, especially the left. The uterine vessels seemed to be healthy."

THE PLACENTA IN ACCIDENTAL HAEMORRHAGE.

The appearances found in the placenta vary with the degree of separation, and the time which elapses between separation and birth of the organ. Where the occurrence/

occurrence of bleeding is quickly followed by delivery, as in many cases of external accidental haemorrhage, the maternal surface of the placenta is usually partially covered by loose fresh blood clot, the tissue underlying which may be seen on section to be compressed, and may show a moderate degree of congestion or mottling; beyond this, there is little or no naked eye difference between the separated portion and that which has remained attached. In some cases the whole placenta appears paler than normal. (see Cases 21 to 25) Microscopically the only change present at this stage is a minor degree of congestion in the vessels of the chorionic villi; this feature is not constant.

In a larger group of cases a sufficient time elapses between the onset of haemorrhage and delivery to allow of the development of definite and characteristic appearances, so that the separated portion of placenta is now clearly defined from that which has remained attached. The best example of this type is the retroplacental haematoma, subtending which there will always be found an area of infarction, of the early, intermediate or late type, according to the age of the clot, and presenting naked eye and microscopic appearances identical with those already described under the pathology of infarction.
(see Plates III, V fig.2, and VII)

THE RELATION BETWEEN ACCIDENTAL HAEMORRHAGE AND TOXAEMIA.

The frequency of albuminuria in accidental haemorrhage is given by different authors in figures varying from 30 to 80 per cent. In my own series the ratio is twenty times in a series of twenty-five cases - i.e. 80%.

This common association strongly suggests either that the haemorrhage results from the toxaemia, as is commonly urged, or that the haemorrhage precedes, and through the coincident placental infarction, originates the toxaemia. If evidence can be produced to show that the onset of bleeding is independent of toxaemia, it must go far to strengthen the thesis which I am attempting to establish. The following considerations render the validity of the common interpretation questionable.

(1) If accidental haemorrhage is provoked by the common toxaemia of the later months of pregnancy, it should occur with special frequency in primigravid women; it is, however, much rarer in these than in multiparae. In my series less than 25 per cent were primigravidae; the average parity was 5.3.

(2)/

(2) In a certain proportion of cases, especially those in which after the onset of haemorrhage delivery is rapidly completed, there may be no evidence of toxaemia; five of my cases (20 per cent) were of this nature (see Cases 21 to 25). It may be urged, of course, against this argument, that cases of toxaemia in which the urine till a comparatively late stage remains albumen-free are not unknown; such however are extremely rare.

(3) That the toxaemia is secondary is shown by the fact that one may occasionally observe its development subsequent to the haemorrhage. In two of my cases (8 per cent) an analysis of the urine within a few hours of the bleeding was negative, whereas at a later examination an albuminuria was present. (see Cases 14 and 15). (An albuminuria develops so rapidly after premature separation of the placenta, however, that it is usually present by the time the patient is admitted to hospital.)

(4) A study of the aetiology of accidental haemorrhage, and especially of the morbid changes present in cases of the concealed variety, suggests strongly that in many cases a mechanical factor/

factor is in operation. One hesitates to quote trauma as an aetiological factor of importance; in three of my cases, however, (Nos. 8, 9, and 21) a history of trauma was given, and in two the urine contained a considerable deposit of albumen. In favour of a mechanical theory of origin, evidence more reliable and convincing is obtained by a study of the changes in the uterus in cases of concealed accidental haemorrhage, of which, it may be recalled, severe toxaemia is a common accompaniment. Numerous observers have drawn attention to the resemblance which the intensely congested, haemorrhagic uterus found in such cases bears to a pedunculated ovarian or fibromyomatous tumour with acute torsion of the pedicle. Young has described a case in which he found extensive bilateral thrombosis of the ovarian veins, and has suggested such a blockage as a possible factor, and in a case recently operated on in the Royal Maternity Hospital bilateral thrombosis of these vessels was also present. As I shall show later, it is possible to produce in animals the exact counterpart of concealed accidental haemorrhage by interference with the venous return from the uterus. The distribution of the haemorrhage in the uterine wall is also suggestive. The extravasation, as Willson has shown, tends to reach its acme near the peritoneal,/

peritoneal, rather than towards the decidual aspect of the uterus. (see Plate II fig 2) If the important aetiological factor were some haemorrhagic toxin, it appears reasonable on anatomical grounds to assume that the haemorrhage would be retroplacental; it is however unlikely that with retroplacental bleeding the blood would be forced through the uterine wall rather than along the line of lesser resistance behind the membranes.

It is of special interest to note the resemblance which the appearance of the uterine wall in concealed haemorrhage shows to changes found in cases of so-called spontaneous rupture of the uterus, in which fragmentation of muscle and extensive vascular infiltration of the muscular wall also occur. W.A. Scott, describing two such cases, writes: "In the light of the findings of J. Whitridge Williams in cases of accidental haemorrhage where there was a diffuse haemorrhagic infiltration separating the uterine muscle fibres, it is possible that a common underlying cause may account for both early spontaneous rupture and premature separation of the normally situated placenta". Spontaneous rupture is essentially a mechanical process, and if Scott's suggestion is well-founded the significance is obvious.

(5)/

(5) Willson, although he believes that a general maternal toxaemia is the important causal factor, admits that "if we accept the hypothesis that the general toxaemia is primary, it becomes necessary to assume, it would seem, that we are dealing with a toxin of haemorrhagic properties with a selective action on the tissues most involved, that is, the decidua, myometrium, parametrium, perimetrium and ovaries. A toxin with such diversity of chemical affinities seems unlikely."

I have endeavoured in the preceding pages to disprove the theory that accidental haemorrhage is caused by a maternal toxaemia. It was shown at the outset that the relationship between the two conditions is so intimate that the conditions must be inter-dependent. The logical conclusion is that the toxaemia is the result of necrotic changes which have been induced in the placenta by premature separation.

Where birth of the placenta follows quickly on the onset of bleeding sufficient time is not allowed for the development of infarction; toxaemia is therefore inconspicuous, and if present is represented by a slight transient albuminuria. In this category are numbered most cases of external bleeding. On the other/

other hand where the placenta has been retained in the uterus for some time after the occurrence of haemorrhage, the development of infarction is invariable. The best example of this type is the retro-placental haematoma, subtending which, as already stated, there will always be found an area of infarction. Toxaemia is the dominant feature of this class of case. The most severe toxaemias in my series of accidental haemorrhage belong to this class. It includes four cases of eclampsia.

SHORT ANALYSIS OF CASES OF ACCIDENTAL HAEMORRHAGE.

My series consists of twenty-five consecutive cases. Six of them (24 per cent) occurred in primigravidae, nineteen (76 per cent) in multiparae; the average parity was 5.3.

The cases were grouped as follows:-

(1) Cases with a history of toxaemic symptoms prior to the occurrence of bleeding (exclusive of cases of eclampsia):- There were five cases of this nature (20 per cent). In all of these more or less old-standing necrotic lesions were found in the placenta at birth, the majority of these subtending old retroplacental haematomata (see page 146).

(2) Cases with no history of toxaemic symptoms preceding the bleeding, but in which on admission to hospital albuminuria was present (exclusive of cases of eclampsia):- There were eight cases in this category (32 per cent). In three of the patients the albuminuria was associated with other evidences of toxaemia, oedema of the face, headache etc., whilst in one, a case of concealed accidental haemorrhage (Case 6), the toxic symptoms/

symptoms were so severe that the patient's condition caused considerable anxiety.

(3) Cases in which the urine was albumen-free on admission but in which albuminuria was subsequently present:- Two such cases were observed (8 per cent).

(4) Cases of accidental haemorrhage combined with eclampsia:- There were five cases of this type (20 per cent). One was a case of severe concealed accidental haemorrhage; in the other four, large retroplacental haematomata were found.

(5) Cases in which the urine remained albumen-free throughout:- This group comprised five cases, (20 per cent); all were cases of external accidental haemorrhage, in which delivery was completed within a few hours of the occurrence of bleeding.

PLACENTA PRAEVIA AND TOXAEMIA.

It sometimes happens that in placenta praevia the detachment of the placenta commences some days before the delivery of the uterine contents. If the thesis I am attempting to substantiate be correct such cases should be associated with a toxaemia. It was decided therefore to conduct an investigation along these lines.

Toxaemia has, so far as I know, never been regarded as bearing any aetiological relationship to placenta praevia, though a number of cases, in particular one by Holland, have been recorded in which low implantation of the placenta was combined with albuminuria. The concurrence has been, however, considered as a chance phenomenon. Recently Jardine and Kennedy have reported a series of eleven cases of toxaemia so severe as to lead to complete suppression of urine, and in two of these there was placenta praevia. These conditions are each so rare that unless there is a possible mutual dependence they should occur together only once in several hundred thousand cases.

A rise in blood-pressure is probably the earliest/

earliest definite sign of a toxaemia that we possess. In cases of severe haemorrhage however, despite the presence of toxaemia this indication may obviously be wanting, and in this investigation the presence of albumen in the urine was taken as a test.*
In all the cases the bleeding had commenced before admission of the patient to hospital.

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* For this investigation, as for the similar investigation of the cases of accidental haemorrhage, a catheter specimen of urine was obtained as soon as possible after the admission of the patient to hospital and also at subsequent intervals thereafter.

SHORT ANALYSIS OF CASES OF PLACENTA PRAEVIA.

My series consists of seventeen cases of placenta praevia which, with the exception of cases 29 and 32, were observed consecutively. Two of the patients (12 per cent) were primigravidae, fourteen (88 per cent) were multiparae; the average parity was 6.8.

The cases were grouped as follows:-

(1) Placenta praevia with albuminuria on admission, but with no toxaemic symptoms preceding the haemorrhage, (exclusive of one case of eclampsia):- There were seven cases of this nature (43 per cent). In one case only a trace of albumen was present and quickly disappeared. In two it increased from a trace at the first analysis to a considerable deposit at subsequent examinations. In one case, an XI-para, labour was induced at the seventh month for placenta praevia; the patient's health, previously perfect, now deteriorated, and violent headaches and other evidences of toxaemia such as marked albuminuria developed. During the puerperium her condition only partially improved, and some months later she was admitted to the medical side of the Royal Infirmary/

Infirmary with an acute recrudescence of kidney mischief from which she died. In one case the occurrence of haemorrhage was followed by a train of symptoms suggestive of acute yellow atrophy; the patient died, but permission for a post-mortem examination was refused.

(2) Placenta praevia in which the urine was clear on admission but in which albuminuria was subsequently present:- There was one case of this type (6 per cent).

(3) Placenta praevia combined with eclampsia:- One such case was observed (6 per cent), (see Case 34); the diagnosis of eclampsia was confirmed post-mortem.

(4) Placenta praevia in which the urine remained albumen-free throughout. There were eight cases in this category. (47 per cent).

It is pointed out that although in the complete series albuminuria was present in 53 per cent of the cases, in the consecutive series of fifteen cases (Cases 29 and 32 being omitted) its incidence falls to 46.7 per cent.

Between the 4th January and 3rd September 1923, forty-two/

forty-two cases of placenta praevia were admitted to the Royal Maternity Hospital. In twenty-seven of these an analysis of the urine was made on one or more occasions subsequent to admission, a catheter specimen being, with few exceptions, obtained for purposes of examination. In twelve cases (44.5 per cent) albuminuria was found. In three cases only a trace of albumen was present and rapidly disappeared; in three cases the amount of albumen was observed definitely to increase; in two cases, placenta praevia was combined with eclampsia; in one of these the combination was probably of the nature of coincidence, for the placenta was extensively diseased and there was a long history of toxaemic symptoms; the patient was a primigravida. In the other case, however, the patient, a II-para, had enjoyed perfect health until the onset of haemorrhage; toxic symptoms very rapidly developed, and before delivery had been completed, an eclamptic convulsion had occurred. Between the onset of haemorrhage and birth of the placenta twenty hours elapsed. After delivery the toxaemia rapidly subsided and at the end of one week the urine was practically albumen-free.

These records are striking and, although the series is too small to warrant any far-reaching conclusions, go towards the confirmation of my argument. The/

The observations made arouse the suspicion that, in the past, the toxaemia which apparently is liable to occur in placenta praevia has been frequently overlooked, any symptoms being attributed to the collapse and the anaemia of haemorrhage. As a control I examined four cases of severe haemorrhage, other than obstetrical, and in each case the urine gave negative findings.

The association of albuminuria with placenta praevia is admittedly less frequent and less conspicuous than with accidental haemorrhage; my ratio of 46.7 per cent no doubt considerably exceeds the average findings. If placental separation, provided the case does not rapidly terminate in labour, induces a toxaemia, how is one to account for this relative infrequency of toxaemia in placenta praevia? There are two considerations which may be adduced in explanation. (a) For the production of a moderate degree of toxaemia it is probably necessary that a considerable extent of the placenta should undergo degeneration. Young has suggested that for an eclamptic seizure it is necessary that one half or one third of the placenta be infarcted. In the majority of cases of placenta praevia, however, the area of separated placenta is comparatively small and the resulting toxaemia correspondingly inconspicuous. For the same reason toxaemia in abortion

or/

or in extrauterine pregnancy is seldom met with.
(b) As compared with placental separation in accidental haemorrhage, the possible channels for the exit and absorption of toxic products in placenta praevia are comparatively limited. In the former, best exemplified for my purpose in the retro-placental haematoma, the area of degeneration is completely surrounded with living placental tissue and a ready access into the systemic circulation of any toxic material is thus allowed. In placenta praevia however, if one excepts the completely central variety, the separated portion is in limited contact with healthy placenta and the diffusion of poisonous material elaborated in the infarcted area is inevitably less free.

OTHER CAUSES OF PLACENTAL DEGENERATION AND TOXAEMIA.

It has been shewn above that mechanical factors may cause a detachment of the placenta from the uterine wall, and, as in certain cases of placenta praevia and accidental haemorrhage, such a mechanical detachment is the cause of the degeneration that ends in toxaemia. It often happens, however, that in cases of ordinary infarction of the placenta the exact cause of the impairment of the maternal blood supply is difficult/

difficult or impossible to discover by an anatomical examination. In some such instances, a thrombosis is found in the decidual vessels; Young believes that this factor operates in a number of cases but admits that it is impossible of proof, for one cannot tell from the microscopic appearances whether the thrombosis has preceded or followed the necrosis. If it be granted that, in the absence of a mechanical separation of the placenta, such as occurs in placenta preavia and in certain cases of accidental haemorrhage, thrombosis of the corresponding maternal vessels is responsible for the development of infarction, on what does the occurrence of this exaggerated* thrombosis depend? Two alternative explanations may tentatively be offered:-

(1) Attention has already been directed to a paper published in 1919 by Talbot in which, as the result of clinical observations, he expressed himself convinced that, in eclampsia, a septic focus was, in some form, invariably present. In recent years La Vake, Mosher, Shoganoff and others have also drawn attention to the frequent association of chronic sepsis with albuminuric and eclamptic toxaemia.

In/

* Goodall has shown that, in the later weeks of pregnancy, thrombosis of the decidual vessels is normally found.

In a second paper published in 1922 Talbot refers to the frequency of placental infarction in such toxaemia, and adduces very suggestive histological and clinical evidence to show (a) that this lesion is secondary to a haemorrhagic lesion (of the nature of thrombosis) in the maternal blood vessels of the placental site, (b) that the primary lesion in the maternal blood-vessels is infectious in origin, and (c) that the infection is haematogenous, its source being generally found in the teeth or tonsils. Thrombosis in the peripheral veins is commonly infective in origin, and is met with in such conditions as rheumatic fever, measles, influenza, pneumonia and typhoid fever. (Osler)

Talbot admits, however, that bacteriological methods to prove that the infarct is infective in origin have not proved successful.

(2) Is it possible that the increased intra-abdominal pressure, which Paramore claims to have shown is present towards full term, especially in primigravid women, (in whom toxaemia is specially liable to develop), may tend to cause venous stasis with consequent thrombosis? The question cannot be answered until we have a more intimate knowledge of the vascular conditions that obtain in the abdomen and pelvis during pregnancy.

THE ANALOGY OF "TRAUMATIC TOXAEMIA"; POST-PARTUM ECLAMPSIA.

When Young propounded his infarction theory in 1914, the conception that products elimitated from the disintegration of tissues at such an early stage could be toxic was a new one in pathology. This worker was able to show that autolysis of the human placenta increased its toxicity to the lower animals, and claimed to have reproduced in lower animals, by the injection of early autolytic products of the placenta, a disease exhibiting the classical features of human eclampsia.

Since Young's original investigations it has become recognised that similar factors operate in other diseased conditions and appear to afford, by analogy, confirmation of his thesis. In particular I would direct attention to researches on the origin of shock and more especially on the pathogenesis of what is known as "traumatic toxaemia".

The frequent association of shock with extensive muscle injury was recognised during the war. That the severe shock observed in these cases was largely contributed to by a toxaemia resulting from the liberation of toxic products of damaged tissue was evidenced clinically by the improvement, immediate and/

and maintained, which followed removal of a badly lacerated limb, or the application of a tight tourniquet when the patient was too shocked to stand operation. The experimental investigations of Professor Bayliss and Lt.-Col. Cannon have shown that the fission products of muscle are toxic in nature. Where extensive muscular injury was produced in an animal, a "traumatic toxaemia" resulted which was shown to be due to the absorption of some toxic substances given off by the injured tissues, and to be independent of a nervous stimulation by its occurrence in cases where the nerve supply of the part had been completely severed, and by its absence in cases where the nerves were intact but the blood-vessels tied. In cases where a tight tourniquet was applied above the level of injury, no reaction appeared until after the release of the tourniquet; on the other hand, where a reaction had been allowed to appear, the application of a tourniquet was immediately beneficial. (Apart from the extent to which skeletal muscle is involved in war wounds there seems to be no ground for awarding it a special position as a source of toxic products of injury; Cannon has produced similar results by damaging the liver (Dale)). Similar observations have been made by Delbet and Quénu, who/

who have further shown that the animal might die immediately or within a short time from an apparent over-stimulation of the nervous system; or it might live for hours or a day or more, and then die from damage to the liver or suprarenal capsules.

While caution must be shown in the application of these findings to eclampsia, there are several points at which the analogy appears to hold. The non-appearance of toxaemia in those cases of accidental haemorrhage, where the haemorrhage extends so rapidly as to cause a complete separation of the placenta, may correspond to the absence of reaction in those experiments where a tourniquet is applied before the limb is crushed; in both cases access of disintegration products into the systemic circulation is prevented. Similarly the improvement which, in albuminuria or eclampsia, generally follows delivery or intra-uterine death is in common with the benefit which in the animal experiments follows the application of a tourniquet after symptoms of shock have appeared; in neither case is further absorption of toxin possible.

It is with regard to post-partum eclampsia, however, that the analogy is of greatest interest and suggestion. The problem of post-partum eclampsia is a difficulty which must be faced in any attempt to explain/

explain the phenomena of this disease. A consideration of the sequence of events in eclampsia makes it possible that the end stages are to be accounted for by the absorption of products of autolysis of such tissues as the liver and possibly the kidney, and are not the immediate or direct results of a placental poison. There is, as it were, a secondary intoxication superimposed on the first, and for its evolution, some hours or even days may be required. If this explanation be correct, it accounts for the occasional delay of the final stages of toxaemia till the post-partum period.

The possibility of a delayed action of this nature is supported by the analogy of the toxic effects of damaged muscle. War surgery has shown that where an extensive muscular injury occurs, the patient may shortly afterwards succumb to "primary" shock, nervous in origin, or he may recover and twenty-four or forty-eight hours later die as the result of an intoxication with harmful tissue disintegration products. The researches of Bayliss, Delbet and others referred to above have also demonstrated that in animal experiments death may be delayed for a day or more, the animal eventually succumbing to the effects of disintegration of the liver and suprarenal glands.

There may also be cited as analogous the action of certain chemical poisons such as phosphorus or chloroform where a day or more may elapse between the introduction of the poison and the development of toxaemia.

EXPERIMENTAL INVESTIGATION.

While the observations which I have made in the preceding pages appeared well founded on clinical and anatomical grounds, it was realised that the argument in favour of a placental theory of origin in eclampsia would be strengthened, could positive evidence from the results of animal experiment be obtained. It was decided, therefore, to carry out an investigation of this nature. Three groups of experiments were conducted, the animals employed being guinea-pigs, and numbering twenty-two in all. I regret that owing to the difficulty of obtaining pregnant animals a larger number of experiments was impossible. Of the animals employed ten were pregnant and twelve non-pregnant. The former were taken from "stock" and operated on when from the size of the abdomen it was found that a sufficiently advanced stage of gestation had been reached. In no case was the date of insemination ascertained, nor was a knowledge of the exact stage of pregnancy arrived at considered necessary for my purpose.

GROUP I. GENERAL PURPOSE OF EXPERIMENTS.

This was, in the first instance, to produce premature separation of the placenta by interfering with/

with the venous return of the uterus, and secondly, to investigate whether thereby lesions could be produced in the kidney and liver, similar to those found in the human, in cases of accidental haemorrhage associated with toxaemia. If placental separation could be caused in this manner, it would strengthen the view that in the human such separation may be mechanical in origin; further, if, as the result of the experiment, degenerative lesions were found in the kidney and liver, strong confirmatory evidence would be forthcoming that in the human, toxaemia is the consequence rather than the cause of placental separation. The principle of the experiment was based on the morbid appearances found in cases of concealed accidental haemorrhage, and also on the work of Morse who, operating on pregnant cats, was able to produce extensive uterine haemorrhage by ligation of the retro-uterine veins.

Anatomical Considerations:-

In the pregnant uterus of the guinea-pig, the number of gestation sacs contained varies from one to five; in the animals which I employed the average number was 2.7. The uterus is suspended from the posterior abdominal wall by a mesometrium or broad ligament, in which the uterine blood-vessels run. Proximally these vessels are/

are linked up with the hypogastric system. Distally they usually become arranged in groups, the number of groups corresponding to the number of pregnant sacs in the uterus. Between neighbouring groups a few anastomosing vessels run. Each vascular group is made up of a varying number of small arteries and veins, which, as the uterine wall is approached, converge on the neighbourhood of a placental attachment. Throughout their course in the mesometrium each corresponding artery and vein is closely associated, and in the dissection and isolation of the veins, which was an essential to the success of the experiment, injury to one or other vessel was difficult to avoid. After reaching the uterus wall further branching occurs, a proportion of the blood-vessels ramifying over the uterine wall, a part penetrating the wall to enter the maternal part of the placenta.

Technique:-

The animal was anaesthetised with ether, and was then fixed down on its back to a wooden operating platform. The abdomen was shaved and thoroughly cleansed with iodine. The instruments employed were sterilised in pure lysol and then placed in weak lysol solution. Two squares of linen fixed to the abdomen with small towel-clips shut off the operation area. The abdomen was then opened in the/

the middle line by a linear incision about two inches long just above the pubes. The pregnant uterus which usually presented itself at the wound was gently expressed from the abdomen, and was at once wrapped in gauze wrung out of warm, moist, very dilute lysol solution; there being as little direct handling as possible. It was necessary completely to expose the broad ligament so that the most suitable vessels for ligation might be ascertained. The next step consisted in the dissection and isolation of one or more groups of veins, and, as mentioned above, the vessels are so slender and their association with corresponding arteries so intimate, that injury was difficult to avoid. A round intestinal needle, the point of which had been filed blunt, was found to be the most suitable instrument. The needle was already threaded so that ligation might be completed without loss of time. Fine linen thread was the material for ligature employed. The uterus was then gently returned to the abdomen and the abdominal wall closed with a through-and-through "blanket" suture of linen thread, collodion and cotton wool being applied as a dressing to the wound.

DETAILS OF EXPERIMENTS IN GROUP I. SIX EXPERIMENTS.

EXPERIMENT I.

On the abdomen being opened, the uterus was found to contain three pregnant sacs, towards the placental attachment of each of which a large leash of blood vessels ran in the mesometrium; neighbouring leashes were linked up by a few anastomosing channels. One group of veins, consisting of one large and two smaller vessels, was ligated. Immediately afterwards, the veins over the corresponding placenta were seen to be greatly engorged, and the uterine wall in the neighbourhood rapidly became congested and cyanotic. The uterus was watched for about five minutes, at the end of which time the cyanosis was less intense but more diffuse. The uterus was then replaced and the abdomen closed. The duration of the operation was seventeen minutes. The animal was seen at intervals of eight and twenty-three hours after operation; recovery was apparently complete.

After twenty-six hours the animal was killed. The uterus showed a diffuse congestion, moderate in degree, and only slightly more pronounced in the neighbourhood of the placenta the circulation of which had been interfered with. Apparently an efficient collateral circulation had been established. On

opening/

opening the uterus it was found that no haemorrhage had occurred into its interior; all three placentae were still firmly attached, it was noticed, however, that the affected placenta was much more cyanotic than the other two, a feature which was specially evident when a cut section of the organ was made. Cultures were taken from the peritoneal cavity and proved negative. The bladder contained a small quantity of urine, which was aspirated by means of a hypodermic syringe; a faint trace of albumen was present.

Microscopic Examination.

Kidney: The section shows both cortex and medulla. The medulla is healthy. In the cortex early degenerative changes have in places occurred. Here and there the epithelial cells of the convoluted tubules are swollen and towards the free margin are breaking down. The nuclei are in places granular and partial loss of nuclear staining has occurred. The glomeruli are in the majority of instances healthy.

Liver: The liver appears healthy.

Uterine Wall: No haemorrhage into the uterine wall has occurred. The blood vessels throughout are much distended, otherwise the appearances are normal.

EXPERIMENT II.

The uterus was found to contain two pregnant sacs, a group of blood-vessels running towards each placental area. One group of veins, comprising four small vessels, was ligated. During the dissection a vein was torn across, considerable haemorrhage taking place; ligatures were applied proximal and distal to the rent. Before the abdomen was closed, marked congestion and cyanosis was present over about one half of the uterus, being most marked in, but not confined to the posterior surface. The operation lasted nineteen minutes. The animal was seen at intervals of six and seventeen hours after operation. Its condition was fairly good.

Twenty hours after operation the animal was killed. The uterus was cyanotic over a large extent of its surface, especially in the neighbourhood of the previous interference. The veins in the broad ligament, other than those which had been ligated, and also the ligated vessels distal to the ligatures, were considerably engorged. On opening the uterus a small quantity of fresh blood clot was found in its interior and one placenta was partially detached, the other was firmly adherent. No difference in congestion between the two placentae, or between the attached/

attached and separated portions of the affected placenta was observed.

Cultures taken from the peritoneal cavity showed a mild growth of staphylococci. The bladder was empty.

Microscopic Examination:

Kidney: Early degenerative changes have occurred in the cortex; the epithelial cells lining the convoluted tubules are swollen so that the lumen of the tubules is narrowed, and in places desquamation has occurred so that the lumen is partially filled with granular debris. In the more affected areas granular degeneration of the nuclei has occurred. The glomeruli are in the main healthy, although here and there the epithelial capsule has disappeared.

Liver: The liver is healthy in appearance.

Uterine wall: The blood-vessels throughout are considerably congested; otherwise the tissue appears normal; there is no evidence of haemorrhagic extravasation.

EXPERIMENT III.

On the abdomen being opened the uterus was found to contain four pregnant sacs. The venous return of three of these, comprising three large and a number of smaller veins was ligated. Distal to the ligatures the vessels rapidly became distended, the congestion being specially marked in the neighbourhood of the placental site, and quickly extending over the greater part of the uterus. The other vessels in the mesometrium, both arteries and veins, in a short time became much engorged. The operation lasted twenty-two minutes. The animal was seen seven hours after operation and appeared to be recovering well. When seen sixteen hours after operation, however, it was drowsy and listless; after a further five hours it was obviously dying and was killed.

On the abdomen being re-opened, a small quantity of blood stained serum was found in the peritoneal cavity. The uterus was diffusely congested and seemed distended; here and there petechial haemorrhages had occurred. On opening the uterus, it was found that haemorrhage had taken place into its interior. One placenta was completely detached, two were partially detached; the fourth, the blood supply of which had not/

not been interfered with, was still adherent to the uterine wall. A small quantity of urine was present in the bladder and contained albumen.

Microscopic Examination:

Kidney: The appearances are roughly similar to those described in the preceding experiments; the degenerative changes, however, are more widespread and more advanced; desquamation of the cells lining the convoluted tubules is marked, and in places the lumen of a tubule is completely filled with cellular debris. A few of the glomeruli appear shrunken, and here and there the epithelial capsule has been shed.

Liver: Destructive lesions of the nature of a granular degeneration of the protoplasm of the liver cells, with partial loss of nuclear staining have here and there occurred; the cell outlines are more or less intact. The change is a diffuse one with no characteristic distribution.

Uterine wall: (1) Section taken from neighbourhood of mesometrial attachment. The blood-vessels are much distended; in one or two areas haemorrhagic extravasation, separating the muscular bundles, has occurred.

(2) Section taken from a point about two inches from mesometrial attachment. The uterine wall appears normal.

EXPERIMENT IV.

The uterus was found to contain three gestation sacs. With the exception of one or two small vessels, the venous return was completely obstructed, five ligatures in all being applied. Before the abdomen was closed the veins distal to the ligatures had become greatly engorged; the uterus was intensely congested over the greater part of its surface and one or two small punctate haemorrhages under the peritoneum were seen to have occurred. The uterus was gently returned to the abdomen and the abdominal wound closed, the operation having lasted twenty-four minutes. The experiment was carried out at 5 p.m. At 12 midnight the animal was seen by the laboratory assistant and stated to have been restless and showing occasional twitching of the limbs. At 8 a.m. the animal was found freshly dead.

On opening the abdomen a striking appearance of the uterus was found (see plate XI). The organ was distended and extensively congested and haemorrhagic. Widespread splitting of the peritoneal coat had occurred; under the peritoneum there was much haemorrhagic extravasation, and the muscular wall of the uterus was seen to be diffusely infiltrated with blood. The uterus was ligated at either pole and removed entire/

entire (see specimen). Cultures taken from the abdominal cavity showed a mild growth of a coliform organism. Urine drawn off from the bladder contained a large quantity of albumen.

Microscopic Examination:

Kidney: (see microphotograph 19). The section consists almost entirely of cortex which shows marked degenerative changes, which, while widespread, vary in degree of severity in different areas. Cloudy swelling and granular degeneration of the cells lining the convoluted tubules have occurred; the lumen of the tubules is in places much narrowed or obliterated as the result of swelling of its lining cells; the lumen is occupied by faintly staining cellular debris from breaking down of the cells at their free margin. Some of the glomeruli appear healthy, in others complete disintegration has occurred, the glomerulus being represented by an irregular clear space containing a few cellular remains, no trace of the capsule persisting.

Liver: (see microphotograph 18).Advanced & widespread degeneration has occurred. The change consists chiefly in an almost complete destruction of the cell protoplasm, the nucleus and cell membrane/

membrane being least affected. Here and there fusion of neighbouring cells has occurred the intervening cell membranes having disappeared; nuclear degeneration in all stages is also seen. While at no place normal liver tissue is seen, in the neighbourhood of the vessels the degenerative changes seem less pronounced. Differentiation of the liver cells into columns is almost completely lost.

(The post-mortem examination was made about six hours after death).

EXPERIMENT V.

The uterus contained two gestation sacs. All the veins in one vascular group, and two veins (out of four) in the second group were ligated. The usual congestion of the uterus and of the vessels distal to the point of ligation was observed. The operation lasted seventeen minutes. The animal was seen at intervals of three, six and eight hours after operation; at these visits the animal seemed drowsy and listless, but no special untoward symptoms were observed. When visited seventeen hours after operation, death had occurred; this was apparently due to complete obstruction resulting from strangulation and gangrene of a short loop of small intestine, which had herniated through the upper angle of the abdominal incision where a stitch had given way.

On the abdomen being opened, the uterus was found to be deeply congested, and although less haemorrhagic than in the preceding experiment, a number of petechial haemorrhages had occurred. When incised, it was seen that haemorrhage had taken place into its interior; one placenta was almost completely detached, in the other a partial degree of separation had occurred.

Microscopically, the blood vessels in the uterine wall are seen to be much distended; a few localised areas of extravasation are present, one of these is shown to proceed from a ruptured vessel.

EXPERIMENT VI.

On the abdomen being opened the uterus was found to contain three pregnant sacs. The vascular distribution was unusual, the blood vessels coursing irregularly in the mesometrium and not being collected into groups. The venous return was almost completely obstructed, two or three small veins and anastomosing channels being left untouched. During the dissection two small arteries were injured and required ligation. Before closing the abdomen about two-thirds of the uterus was congested and cyanosed, and a small extravasation in the uterine wall over one placental area was observed to have occurred. The operation lasted twenty-three minutes. The animal was seen at intervals of two, five, and sixteen hours afterwards, and, while drowsy and listless, appeared to be recovering from the effects of the experiment. When seen twenty-four hours after operation spasmodic twitchings of the muscles of the limbs and trunk were observed; the animal was lying on its side and, when placed on its feet, at once fell over. About one hour later death occurred.

On re-opening the abdomen a considerable quantity of blood-stained fluid was found in the abdominal cavity. The uterus was deeply congested and numerous areas/

areas of extravasation could be seen; fissuring of the peritoneal coat had occurred in a few places. On opening the uterus it was found that haemorrhage had taken place into its interior. Two placentae were almost completely detached; in the third, separation over a small area was found. All three placentae were deeply engorged. Cultures taken from the peritoneal cavity proved negative. No urine was found in the bladder.

Microscopic Examination:

Kidney: Extensive degenerative lesions are present, affecting principally the convoluted tubules, the lumen of many of which is filled with cellular debris; the nuclei have in places persisted, in other places disintegration or complete disappearance has occurred. Many of the glomeruli are degenerated and shrunken.

Liver: The liver cells are swollen and in places granular degeneration has occurred; as in the other experiments the nucleus and cell-membrane have resisted longest. Here and there neighbouring cells have fused to form irregular cavities through disappearance of the intervening septa. The lesions are diffusely scattered throughout the/

the organ, and are not localised specially to central or peripheral zones. There is no evidence of haemorrhage or thrombosis.

Uterine Wall: The blood-vessels are greatly engorged throughout. In places the muscle fibres have become dissociated by extravasated blood. (Some areas of blood clot in this section suggest artifact formation). (see microphotograph 17).

SUMMARY OF EXPERIMENTS IN GROUP I.

The general purpose of the investigation, which was to cause separation of the placenta by interfering with the venous return from the uterus, and, at the same time, to produce degenerative lesions in the kidney and liver, has been achieved. With the exception of experiment I where no separation took place, and experiment IV where the uterus was preserved unopened, detachment of the placenta, partial or complete, occurred in each case. The amount of separation and the degree of extravasation in the uterine wall were proportional to the degree of interference with the venous return from the uterus; only where this was almost completely obstructed did extensive haemorrhagic lesions result; otherwise an efficient collateral circulation was established. In all cases degenerative changes, affecting mainly the convoluted tubules, were produced in the kidney, and in four cases lesions were found in the liver. The degree of severity of the lesions in these organs appeared to vary with the amount of placental substance detached.

In the interpretation of these results and in their correlation with the morbid changes found in human accidental haemorrhage caution is required.

It has been pointed out that, in the animal experiments, almost complete obliteration of the uterine veins was necessary before widespread haemorrhage resulted, in the human such a degree of interference with the venous return has never been described. While this is so, the changes produced in experiments IV and VI so closely resemble those met with in concealed accidental haemorrhage, as to suggest strongly that, in the production of the latter, venous obstruction may be an important factor.

While, with the doubtful exceptions of experiments IV and VI, no convulsive seizures nor other symptoms which could be regarded as toxaemic were produced, the lesions found in the kidney and liver are suggestive, in that they appear to be the direct consequence of the interference and to vary in severity with the amount of placenta detached; except that in the liver the general distribution of the changes produced is in no sense characteristic, the lesions both in kidney and liver bear more than a superficial resemblance to those found in the human in cases of accidental haemorrhage accompanied by the milder degrees of toxaemia.

In experiment IV, in which the degenerative changes were most marked, the effect of post-mortem autolysis must be taken into account. That this was not/

not primarily or mainly responsible, is shown by the occurrence of similar changes in other experiments in which the animal was killed and a post-mortem examination at once made. Another factor to be considered is the effect of the anaesthetic; as a control, therefore, an animal was anesthetised for twenty-five minutes and killed twenty-four hours later. Microscopically, the liver presented a healthy appearance, the kidney showed early degenerative changes of a mild character. A third possible fallacy is that the lesions may have been infective in origin. During the experiments, however, the aseptic ritual was most carefully observed. Moreover in two of the four cases in which cultures were taken from the peritoneal cavity, negative results were obtained; in a third, there was a mild growth of staphylococci; and in the fourth, the animal had been dead for six hours before a post-mortem examination was made, so that the finding of a coliform organism in the peritoneal cavity was not unexpected. These considerations seem adequately to answer this criticism.

GROUP II. GENERAL PURPOSE OF EXPERIMENTS.

This was the production of degenerative changes in the kidney and liver as the result of direct separation of the placenta.

Technique:-

The preparation of the animal and the earlier steps of the operation were similar to those already described on page 114. After withdrawing the pregnant uterus from the abdomen, the placental areas were searched for and partial separation of one or more placentae accomplished. For this purpose the most suitable instrument was found to be a fine bayonet pointed, narrow bladed, cateract needle, with which the uterus was punctured in an avascular area close to the site of a placental attachment. The junction of the maternal part of the placenta with the uterine wall was then partially cut through and the instrument withdrawn, the puncture in the uterine wall being closed with a fine linen suture, threaded on the smallest size of round needle. The operation was a simple one and was usually completed in less than fifteen minutes.

DETAILS OF EXPERIMENTS IN GROUP II. FOUR EXPERIMENTS.

EXPERIMENT VII.

On opening the abdomen it was found that the uterus contained two pregnant sacs. The placenta of one was partially separated. During the process of detachment haemorrhage from the severed vessels could be observed through the uterine wall. The animal appeared to recover perfectly from the experiment. Twenty-four hours after operation the animal was killed, and the abdomen re-opened. There was no sign of peritonitis; the uterus was slightly congested, especially in the neighbourhood of the injured placenta, behind which, when the uterus was laid open, a small haematoma was found. The placenta was still partially attached to the uterine wall. No separation of the second placenta had occurred. Apart from the operation puncture, the uterine wall showed no extravasation nor other sign of injury.

Microscopic Examination:

Kidney: Early degenerative changes are present, affecting mainly the convoluted tubules, but not limited to them. The principal change is a cloudy swelling of the epithelial cells, so that the/

the lumen of the tubule is in places much narrowed. Here and there the edge of the cells lining the tubule is ragged and irregular. The glomeruli are healthy.

Liver: The tissue is normal in appearance.

(A strip of placenta, showing both maternal and foetal portions has inadvertently been incuded in this section.) *

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* Sections of the placenta were made in this as in all the other experiments; the appearances found, however, were so variable and confusing that no deductions could justifiably be drawn and their description has been omitted.

EXPERIMENT VIII.

The uterus contained three gestation sacs. The placentae of two of these were partially detached. Considerable oozing of blood occurred from one of the punctures made in the uterine wall, but was controlled by stitching. The animal was seen at intervals of two, six, and eighteen hours after the experiment. Recovery was imperfect, the animal lying quiet and making little or no response to stimulation. Death occurred about twenty hours after operation. No twitchings or convulsions were observed before death. Two hours later the abdomen was opened. No sign of peritonitis was found; the uterus was somewhat congested in the neighbourhood of interference, but otherwise appeared healthy. On being opened, a considerable quantity of blood clot was found in its interior; the two injured placentae were still partially adherent to the uterine wall; no separation of the third placenta had occurred.

Microscopic Examination:

Kidney: Destructive lesions are present in the cortex; as in previous experiments, the epithelium of the convoluted tubules has suffered more than the glomeruli. The cells are swollen, and although the outward shape of the tubules is unaltered, in/

in many cases the lumen is much narrowed, and in places partially obliterated; in other places desquamation has occurred and the lumen is occupied by granular debris. Many of the nuclei are disintegrated and stain feebly, others have completely disappeared. The glomeruli are, for the most part, intact; in a few cases, the tufts appear shrunken and their capsular epithelium has in places become detached.

Liver: Degenerative changes are present, and consist mainly in a cloudy swelling and granular disintegration of the cell protoplasm. The cell membrane and the nucleus are, on the whole, less damaged; here and there however the staining power of the nucleus is less than usual, and in places neighbouring cells are fused through breaking down of the intervening membranes. While the changes are not definitely localised to central or peripheral zones, the cells in the centre of the lobules seem, on the whole, to be better preserved.

Uterine Wall: The muscular tissue appears normal; the vessels are not unduly congested, nor is there any evidence of haemorrhagic extravasation.

EXPERIMENT IX.

The uterus was found to contain three pregnant sacs. The attachment of each of the three placentae was partially severed. The experiment was performed at 6 p.m. The animal was seen at 8 p.m. and again, by the laboratory assistant, at 11 p.m.; it seemed to be very feeble and was thought to be dying. About 7.30 a.m. on the following morning the animal was found dead.

On re-opening the abdomen, a small quantity of free fluid was present in the abdominal cavity; the uterus was cyanosed and when incised was found to contain a large quantity of blood clot in its interior; no extravasation into the uterine wall was evident to the naked eye. One placenta had become completely separated, the other two were still partially attached to the uterine wall. In this case death was probably largely due to haemorrhage and shock.

Microscopic Examination:

Kidney: Degenerative lesions, similar to those described in the preceding experiment, are present. Much desquamation of the epithelial cells has occurred, so that the tubules are here and there blocked with debris. In other places the lumen has/

has become obliterated as the result of cloudy swelling of the lining cells. The glomeruli are less affected.

Liver: The liver cells appear swollen and the protoplasm broken down; many of the nuclei are in a state of granular degeneration, and stain faintly. The outlines of the liver cells, with few exceptions, have remained distinct.

EXPERIMENT X.

On opening the abdomen the uterus was found to contain two pregnant sacs. Both placentae were partially detached. The animal was seen at varying intervals up till twenty-four hours thereafter. No untoward symptoms were observed. The animal was killed about twenty-five hours after the experiment was performed.

On re-opening the abdomen, no evidence of peritonitis was present. The uterus showed the usual congestion in the neighbourhood of the punctured wounds, but otherwise appeared healthy; when incised, a considerable quantity of blood clot was found in its interior, and one placenta was completely detached; the other placenta was still partially adherent.

Microscopic Examination:

Kidney: Early degenerative changes are present in places, and affect mainly the convoluted tubules the cells of which shew cloudy swelling and, at their free margins, are in places breaking down. The glomeruli are on the whole healthy. A good deal of haemorrhage is present, irregularly scattered throughout the kidney tissue and probably artifact in nature.

Liver: The liver cells are cloudy, and granular degeneration of the protoplasm has here and there occurred. The lesion is of a mild type.

SUMMARY OF EXPERIMENTS ON GROUP II.

Degenerative lesions were found in all four cases. The series is, however, so small that no conclusions as to what extent of placental separation is necessary to produce toxaemia can be offered; nor can it be claimed that the severity of the lesions in the kidney and liver was proportional to the degree of separation present. To establish these points a much larger series of experiments would be required than I have had opportunity to perform. While in this regard my results are inconclusive, the experiments are of value in that, taken in conjunction with the earlier experiments, they appear to show that, as a direct consequence of placental separation, degenerative changes may be found in the kidney and liver. In both series of experiments the type of degeneration produced was similar, and essentially consisted, in the kidney, of necrotic changes in the epithelial cells of the convoluted tubules, as shewn by their disintegration and loss of nuclear staining; and, in the liver, of a granular degeneration of the cell protoplasm, the nucleus and cell membrane being less affected.

Examination of the uterine wall, in the second series of experiments, provides a point of interest which may be mentioned. In spite of considerable retro-placental/

retro-placental bleeding, there was no evidence of haemorrhage into the uterine wall. This plainly shows that in concealed accidental haemorrhage, the actual separation of the placenta cannot be the primary or essential lesion, nor can it produce the blood extravasation into the myometrium and dissociation of muscle fibres so constantly found. (See pp. 92, 93).

GROUP III.

The general purpose of the experiments was to reproduce toxaemia by the injection of extract of recently infarcted placenta. Placentae from cases of eclampsia, placenta praevia and accidental haemorrhage were employed. In all, eleven animals were injected; in three of these, extract of healthy placenta was used as a control. The method of preparation of the extract was as follows:- As soon after birth as possible, the entire placenta was removed to the laboratory; a portion of recently infarcted placenta was aseptically removed, cut in pieces and placed in a sterile mortar; normal saline solution in the proportion of 1 in 3 by weight was added, and the whole thoroughly ground into an emulsion. The mixture was then repeatedly filtered through fine wire gauze, and was considered ready for injection.

Quantities varying from 5 to 10 cc. of the extract were injected intra-peritoneally. This method was chosen to avoid the production of a fatal result from widespread thrombosis, such as Lichtenstein has shown may follow the introduction intravenously of solid particles (see p. 51).

The results were uniformly negative. In none of the animals did/

did any toxic symptoms appear, nor in those which were killed were any specific kidney or liver lesions found. While such failure is disappointing, two alternative explanations may be offered.-

(1) The extracts were made from areas of infarction visible to the naked-eye. It has been shown, however, I believe conclusively, that the poison responsible for toxaemia is elaborated early in the course of the disintegration process, while the structure of the placenta shows little or no naked-eye change - as witness the occurrence of a fulminating eclampsia with an apparently healthy placenta. In his experimental work, Young discovered that injection of extract of placenta, autolysed for so short a period as one and a half hours, was followed by convulsive spasms and other evidences of toxaemia. On the other hand this observer found that, where autolysis had been allowed to proceed for a few days, the results of injection were negative. The conclusion which suggests itself is that by the time necrosis has evolved into infarction visible to the naked eye, it may no longer constitute a focus of toxaemia, and extracts made from it be innocuous on injection.

(2) In the light of Liepmann's work (see pp. 60, 61), it is possible that the "toxin" is very labile and difficult to preserve, and in the preparation of the extract, the toxic principle may have been lost or destroyed.

CRITICISMS OF THE INFARCTION THEORY.

While most of the difficulties in the way of acceptance of this theory as an explanation of the cause of toxaemia have already been met at different points in my thesis, it has been thought advisable, before submitting my conclusions, to summarise what has been said in regard to the following criticisms, dealing with these seriatim:-

I. How are the variable appearances in the placenta in cases of toxaemia to be explained?

Cases of eclampsia may be divided in two broad groups:- (1) These in which the placenta shows little or no evidence of degeneration. Here the toxaemia has been fulminating in character, coming on without warning during labour or after its completion, and the placenta is born before sufficient time can elapse for the production of degeneration evident to the naked eye. (2) Those in which multiple areas of infarction in the placenta are present. This is the common type and is invariably found in that class of case where eclampsia has been preceded by albuminuria of long standing.

11./

II. If placental separation is the cause of toxaemia, why is it not met with in extrauterine pregnancy, or in abortion?

Young has estimated that for the production of an eclamptic seizure, it is necessary that about one-third of the full-term placenta should be recently infarcted. In neither extrauterine pregnancy, nor in abortion, is such extensive necrosis as a rule possible; moreover in such cases, detachment of the ovum is usually complete at an early stage. On the other hand, I would point out that instances of the combination of extrauterine pregnancy and eclampsia have been recorded; Ebeler in a review of the literature of fifty cases of eclampsia in early pregnancy, mentions three cases in which the gestation was extrauterine. Moreover, the association of albuminuria with abortion is sufficiently frequent to have originated the statement in many text-books that the former is a common cause of the latter.

III. Why is placenta praevia, in contrast to accidental haemorrhage, so seldom associated with toxaemia?

The area of placental separation is much smaller than is common in accidental haemorrhage, and, unless in the central variety, the separated portion is in limited contact with healthy placenta, so that the/

the diffusion of poisonous material via the healthy placenta into the maternal circulation is inevitably less free. For the same reason where the portion of placenta covering the os uteri is a succenturiate lobe no toxaemia is possible; (see Case 40).

IV. With regard to accidental haemorrhage, if the toxaemia is not the cause of placental separation, how are these cases to be explained in which, for a variable period prior to the occurrence of vaginal haemorrhage, symptoms of toxaemia are present?

Many cases of this nature have been recorded, and have been adduced in favour of a toxaemic origin of premature detachment. In no case, however, so far as I am aware, has it been stated that the placenta at birth was healthy. In five cases of this type observed by myself, an examination of the placenta showed retroplacental haematomata, varying in size and age, in all, indicating that, prior to the occurrence of external bending, retroplacental haemorrhage had been taking place; the presence of toxaemia was explained by the fact that the clots were invariably associated with necrotic changes in the underlying placenta. The argument that toxaemia may have been the cause of the internal as well as of the external haemorrhage is beside the point, and has already been met (see pp. 90-94).

V. How is the occurrence of post-partum eclampsia to be explained?

It is probable that in eclampsia the end stages are to be accounted for by the absorption of products from autolysis of such tissues as the kidney and liver, and are not the immediate or direct results of a placental poison. The time which must elapse for the development of this secondary intoxication, may explain the occasional delay of the final stages till the post-partum period. The possibility of a delayed action of this nature is suggested by the analogy of the toxic effects of damaged muscle, and also of the action of certain chemical poisons such as chloroform and phosphorus. (see pp. 110-111).

SUMMARY AND CONCLUSIONS.

1. The more important theories of eclampsia have been critically reviewed, and the lines indicated along which recent research has been carried out.

2. The infarction theory, advanced by Young in 1914, has been explained, and arguments given in favour of its acceptance as an explanation of the phenomena of eclampsia.

3. The relative frequency of infarction in albuminuria and eclampsia has been considered. From an analysis of two hundred and forty-six consecutive deliveries in the Royal Maternity Hospital, it has been shown that infarction and albuminuria are closely associated.

4. The pathology of infarction has been considered in the light of one hundred and seventy-nine placentae examined, in which this form of degeneration was present, and the naked eye and microscopic features described.

5. The factors responsible for infarction have been discussed, Young's contention that its development is dependent on some interference with the maternal blood supply to the part being confirmed.

6. This interference may be brought about by a mechanical detachment from the uterine wall, such as occurs in placenta praevia or accidental haemorrhage, or it may result from thrombosis of the maternal vessels in the uterine wall.

7. While the cause of this thrombosis is uncertain, the observations of Talbot, La Vake and others on the frequency of chronic sepsis in eclampsia, suggest the possibility of its being infective in origin.

8. The intimate association of accidental haemorrhage and toxaemia indicates that, as regards their production, the conditions must be mutually dependent. That toxaemia is not the cause of the haemorrhage is shown (a) by the relative rarity of the latter condition in primigravidae; (b) by the fact that toxaemia is occasionally absent; (c) by the fact that the development of toxaemia may be observed subsequent to the haemorrhage; (d) by a study of the morbid changes present in the uterus in cases of concealed accidental haemorrhage, and (e) by the experimental production of accidental haemorrhage in lower animals. The logical conclusion is that the haemorrhage precedes, and through the coincident placental infarction,/

infarction, originates the toxaemia, this being possible only where delivery is sufficiently delayed to allow of the development of infarction in the placenta.

9. As in accidental haemorrhage, so in placenta praevia toxaemia may occasionally be present as the result of necrotic changes in the separated portion of the placenta. That toxaemia is relatively infrequent and inconspicuous in placenta praevia is explained by the limited extent of separation usually present.

10. For the same reason, eclampsia seldom accompanies abortion or tubal pregnancy.

11. The conception that toxaemia should result from the absorption of early disintegration products of damaged tissues is supported by the analogy of traumatic toxaemia, and in particular by the researches of Bayliss, Cannon, Delbet and Quénu on the toxic nature of the fission products of damaged muscle, the introduction of which induces, in lower animals, changes resembling those found in the liver in eclampsia.

12. The delay in the production of a lethal result in these experiments suggests that, in eclampsia, a/

a similar interval may elapse between the initiation of the toxic process and its clinical manifestation. Such a consideration is offered as explanatory of the occurrence of post-partum eclampsia.

13. Certain apparent fallacies in the infarction theory have been specially considered and explained.

14. The results of a short experimental investigation may be tabulated as follows:- (a) By ligation of the retro-uterine veins in the pregnant guinea-pig it is possible to produce haemorrhage and changes in the uterine wall, closely resembling those present in the more severe forms of accidental haemorrhage in the human. At the same time, degenerative lesions, broadly similar to those present in the toxaemia of pregnancy, are to be found in the kidney and liver of the animal. Similar lesions may experimentally be produced by direct separation of the placenta from the uterine wall.

Confirmatory evidence is thus afforded that where toxaemia accompanies accidental haemorrhage, the former is to be regarded as secondary to the latter, and not vice versa as commonly urged.

(b) Where the placenta is directly separated by cutting through its attachment to the uterus, the/

the haemorrhage which results does not infiltrate the muscular tissue of the uterine wall. This shows that in accidental haemorrhage the actual separation of the placenta cannot be the primary or essential lesion, nor can it produce the blood extravasation into the myometrium and dissociation of muscle fibres so constantly found.

(c) Attempts to produce toxaemia by the injection into animals of extract of infarcted placenta uniformly failed. It is suggested that by the time the degenerative change in the placenta has evolved into the form of naked eye infarction, it may no longer constitute a focus of toxaemia and extracts made from it be innocuous.

APPENDIX.

DETAILS OF CASES.

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A. ACCIDENTAL HAEMORRHAGE.

The cases have been grouped as follows:-

1. Accidental Haemorrhage with a history of toxaemic symptoms prior to the occurrence of bleeding (exclusive of cases of eclampsia). Five cases.

2. Accidental Haemorrhage with albuminuria on admission but with no toxaemic symptoms preceding the bleeding. (Exclusive of cases of Eclampsia): Eight cases.

3. Accidental Haemorrhage in which the urine was clear on admission but in which albuminuria was subsequently present. Two cases.

4. Accidental Haemorrhage combined with eclampsia: Five cases.

5. Accidental Haemorrhage in which the urine remained albumen-free throughout: Five cases.

GROUP I.

Cases of Accidental Haemorrhage with a history of toxaemic symptoms prior to the occurrence of bleeding (exclusive of cases of eclampsia): Five cases.

Case 1. Mrs M. aet. 21 years, primigravida.

Previous history: Except that menstruation had been irregular and at times excessive, patient's general health has been excellent.

History of present pregnancy: L.M.P. 14th August 1919. In January 1920, there was fairly free bleeding for which she was admitted to the Deaconess Hospital; oozing continued for ten days. Bleeding recommenced at the beginning of March, small amounts of blood being lost every day or so for about a fortnight. Beyond weakness, there were at this time no general symptoms. The patient was admitted to the Antenatal Department of the Royal Maternity Hospital on 30th March for haemorrhage; at this time she suffered from headaches and sickness, there was slight puffiness of the hands and face, and the urine contained albumen. A fairly free haemorrhage occurred about 10 p.m. on the 22nd May for which she was admitted to the Maternity Hospital. Labour did not commence till the evening of the 30th May. Delivery was completed at 7.50 p.m. on the 31st. The placenta was/

was firmly adherent and was removed manually under a general anaesthetic. Albumen was present in the urine till five days after delivery.

Placenta: Examination of maternal surface shows the placenta to be fairly extensively diseased with numerous areas of solidified tissue. In one area towards the lower margin of the placenta some old blood-clot is firmly adherent. Covering about one quarter of the maternal surface and loosely adherent to it is a thin film of fresher blood-clot, probably a relic of the haemorrhage which occurred nine days prior to delivery. On cut-section a large portion of the placenta appears normal; one or two old pale infarcts irregular in shape are seen, one of these fairly accurately subtending the old blood-clot on the maternal surface; under the more recent clot the organ is rather congested and in consistence is firmer than elsewhere.

Microscopic Section: Taken through that part of the placenta to which old blood-clot was adherent.

The appearances are those of an infarct probably some weeks old. Towards one end of the section an old blood-clot is seen; in the placenta adjacent to this the villi are closely crowded together, and in places seem to be fused; there is a diffuse coagulum of old-standing in the intervillous spaces; the blood-vessels/

blood-vessels in the chorionic villi are also occupied by old blood-clot. The epithelium covering the villi is degenerated and has in places almost disappeared, in other places the process of disintegration is less advanced and deeply-staining blue granular masses, seen characteristically in the more recent phases of infarction, are still evident. The marked degree of round-celled infiltration between the blood clot and the placental tissue is of interest in view of the history of adherent placenta at delivery.

Case 2. Mrs W. aet 29 years, II-para.

Previous History: During the first pregnancy the patient was treated for some weeks in the Royal Maternity Hospital for hyperemesis. Otherwise she has always enjoyed good health.

History of present pregnancy: L.M.P. 12.12.19. The patient was an in-patient in the Antenatal Department for hyperemesis from the ninth to the thirteenth week; she has never felt really well since, and for a week or two prior to admission has suffered from headaches, dizziness, and oedema of face and hands. She was admitted to the Royal Maternity Hospital at 3.30 p.m. on the 4th August 1920 in a fainting condition; the uterus appeared larger than normal for stage of pregnancy reached, felt tense, and was very tender to touch. A diagnosis of concealed accidental haemorrhage was made. The os admitted three fingers. At 4.30 p.m., very copious bleeding occurred; the os was manually dilated, and a still-born child delivered by version. After temporarily rallying, the patient succumbed to a sudden post-partum haemorrhage at 8 p.m.; the urine was fairly heavily loaded with albumen.

Placenta./

Placenta. Maternal surface irregular and covered by about one-and-a-half pints of recent blood clot; one or two smaller dark clots, older in appearance, are firmly adherent to the maternal surface. On section, the placenta is irregular in colour and in consistence; only a small proportion of the organ has retained its normal appearance. Under the large fresh clot the tissue is much congested, being a deep purple in appearance, i.e. in a condition of recent infarction. Accurately subtending the other clots, infarct formation of older standing is present, the placenta being firm in consistence and brick-red in colour. Towards the foetal aspect a thin zone of apparently normal tissue is found. A few old pale-pink, and white infarcts are present, irregularly scattered throughout the placenta.

Section (1) Through congested area underlying large clot, (see microphotograph No.9).

The villi almost throughout the entire section are closely packed together; in a few areas however they are widely separated by haemorrhage: the villous vessels are much engorged and in places a vessel appears to have ruptured with discharge of its contents into the intervillous space. Here and there a fine flocculent coagulum occupies the inter-villous spaces, in other parts the coagulum is more/

more dense. In one area towards the decidual aspect a small retro-placental clot is present: note that the process of infarction appears more intense in the tissue underlying it (contrast with section (2).

Section (2) Taken from healthy adjoining tissue towards the foetal surface.

In this section the villi are normal, the villous vessels are not distended, there is no coagulum in the intervillous spaces. A few portions of necrotic decidua are to be seen, but these are normally present.

Section (3) Taken through a firm pale-pink infarct.

The appearances are those of a moderately old infarct surrounded by healthy placental tissue, the infarcted area having somewhat shrunk or contracted so that the contrast between normal and diseased is clearly demonstrated. In the infarcted area the villi are closely packed together and in places have fused. The villous vessels are empty and much of the intervillous coagulum has disappeared, the outline of individual corpuscles being difficult or impossible to make out. Nuclear staining in the epithelial layer is now imperfect, although it has not been entirely lost.

Post-mortem/

Post-mortem appearances.

Uterus. (see plate 1.)

Macroscopic appearance of uterus. The surface of the organ is extensively congested and haemorrhagic, the colours varying from red through purple to dark blue or black. The blood extravasation is more marked on the anterior than on the posterior wall and is specially pronounced on the left side, extending here from fundus to lower uterine segment, (the placenta was attached to the anterior wall rather to the left side). In the neighbourhood of the fundus, especially anteriorly, splitting of the peritoneal coat has occurred, the fissures varying in length from one to three centimetres and running for the most part longitudinally; in other places the peritoneum is raised in the form of blebs containing dark blood.

Myometrium: A coronal section made midway between fundus and cervix shews widespread intramuscular haemorrhage present; the extravasation is more pronounced in the neighbourhood of the placental site and towards the decidual rather than the peritoneal aspect. A few punctate haemorrhages are present in parts of the uterine wall at varying distances from the site of placental attachment.

Section (4) From uterine wall in neighbourhood of placental site (see microphotographs Nos.15 & 16). Extensive haemorrhagic extravasation is present; the/

the muscle bundles and fibres are separated widely and in places torn across by inter- and intra- fasicular haemorrhages. In one or two areas degeneration has occurred, being evidenced mainly by loss of nuclear staining; in one area disintegration is pronounced, a portion of muscle being represented by a faintly staining mass of vacuolated tissue surrounded by blood clot.

A considerable degree of oedema is present.

Section (5) From uterine wall opposite (about four inches from) placental site. Here there is also evidence of intramuscular haemorrhage, less widespread however than in the preceding section; oedema is marked however and areas of necrosis are evident.

Blood vessels. Congestion, especially of the veins, is present. A large haematoma occupies the left broad ligament, and extends into the pouch of Douglas behind and into the utero-vesical pouch in front. The left ovarian vein is plugged by a thrombus, but whether of ante- or post-mortem formation is difficult to say.

About half a pint of blood-stained fluid was found in the peritoneal cavity.

Kidneys. Both organs are larger and paler than normal, and on microscopic examination degenerative changes/

changes are present in the cortex, cloudy swelling and fatty degeneration having occurred in the epithelial cells of the convoluted tubules. No areas of haemorrhage or of necrosis are evident.

Liver. Beyond a diffuse fatty change nothing of note is observed.

Case 3. Mrs T. aet. 43 years, VII-para.

Previous History. Scarlet fever, aet. 11 years, bed seven weeks; previous pregnancies and labours all normal.

History of present pregnancy. L.M.P. 20th August 1910. The patient enjoyed good health till an attack of bronchitis about the middle of April, which kept her in bed for four or five days. For a week or two before admission she had suffered from headaches and some puffiness of the eyes in the morning, and swelling of her hands and feet were noticed. On 11th May 1920, about 3 p.m., without any obvious cause, there was a sharp haemorrhage; on the following day oozing continued. Labour commenced on the evening of the 12th. The patient was admitted to the Royal Maternity Hospital about 12.30 a.m. on 13th May as a case of accidental haemorrhage, bleeding fairly freely on admission; a living female child was delivered at 3.5 a.m., the placenta being expelled immediately afterwards.

Urine. At the time of delivery the urine contained a considerable quantity of albumen; one week later, no albumen present. Puerperium uneventful.

Placenta. The maternal surface is covered over half its area by a large fairly fresh blood clot loosely/

loosely adherent. Towards one edge of the placenta, covering an area about two inches square, is some older blackish clot, adherent but not organised. Sectioned longitudinally and held under running water, the placental tissue under the larger clot is seen to be compressed and deep red in colour. Under the older clot the placental substance is thinned out, congested, and has lost its normal spongy consistence, being firm and leathery to the touch. The rest of the organ is considerably paler than normal.

Microscopic Section:- Taken through the older infarcted area. The villi are much more closely crowded together than normal; in many places there is evidence of proliferation of the syncytial nuclei, showing as granular masses of deeply staining tissue; in other places nuclear staining is absent, indicating a more advanced stage of epithelial degeneration. The villous vessels are turgid, in some places the congestion being so marked that the stroma is much compressed. Here and there rupture of a villous vessel is seen, with haemorrhage into the intervillous space. In many areas the intervillous spaces are free from blood-clot, in a few places a fine fibrinous deposit is observed.

Case 4. Mrs T. aet. 27 years. IV-para.

Previous history: Nothing to note as regards general health. All previous pregnancies and labours have been normal, with the exception of the fourth which was complicated by accidental haemorrhage, unaccompanied by any symptoms of toxaemia

History of present pregnancy: L.M.P. 5th August 1919. The patient's health was excellent until about one month before admission when she began to suffer from headaches and "faint turns"; oedema was occasionally present. No eye symptoms nor epigastric pain were complained of. She was admitted to Royal Maternity Hospital at 1.45 p.m. on the 27th August 1920, with the history that a severe vaginal haemorrhage had occurred two hours previously. On admission the patient was very collapsed and presented the usual symptoms and signs of severe blood loss. She was delivered of a still-born female child at 6.30 p.m. The placenta was expelled immediately after the birth of the child.

Urine: 27.4.20. Abundantly loaded with albumen.

29.4.20. Still a heavy deposit.

4.5.20. Still a trace.

6.5.20. Clear.

Placenta./

Placenta: The maternal surface of the organ is covered by a large comparatively fresh blood-clot, on the removal of which areas of older partially organised clot are seen. On cut-section, the placenta is seen to be extensively diseased; in places its substance appears to have been eaten into by haemorrhage almost to the foetal surface. Infarcts of all ages, irregular in size and shape are present; the largest of these is of the more recent type and more or less accurately subtends a clot adherent to the maternal surface.

Case 5. Mrs O. aet. 36 years. VII-para.

Previous history. Nothing to note. Pregnancies and labours all normal.

History of present pregnancy. L.M.P. 25th August 1920. The patient's health throughout pregnancy has been poor; morning sickness was excessive and prolonged; since September she has felt weak and "run down". For two or three weeks previous to admission headaches and eye symptoms have been complained of, and oedema of the hands and feet has been present. Early on the morning of the 8th January 1921, she wakened up with the bed soaked with blood. During a twenty-mile journey to the Royal Maternity Hospital in an ambulance she was delivered of a still-born child, the placenta following immediately afterwards.

Urine. 8.1.21. Almost solid with albumen.

12.1.21. Albumen still present in moderate amount.

18.1.21. Urine almost clear.

Placenta. Very irregular in shape and consistence; the maternal surface is covered over a considerable area by a thin film of blackish adherent blood-clot. Cut-section under running water shows the placenta to be irregularly mottled; under a shallow depression the size of a crown piece occupied/

occupied by adherent black clot the placental tissue is markedly congested and of the consistence of liver. Scattered throughout the substance of the placenta, especially towards the maternal surface, are numbers of cyst-like spaces occupied by round dark clots. Underlying several of these haematomata the placenta is infarcted. A few old pale infarcts are also seen.

Case 6.* Mrs F. aet. 34 years. IV-para.

Previous History. The first labour was complicated by severe eclampsia, the child being still-born. In each of the three subsequent pregnancies albuminuria developed about the 6th month but the condition was kept under control by careful dieting. Pregnancy went to full-term in each case, the children being all born alive and healthy, and in each case the albumen disappeared very shortly after the labour.

History of present pregnancy. L.M.P. about 14th February 1922. The urine was repeatedly examined by her doctor, and no albumen was ever found. The date of the last analysis was the 22nd of September 1922. On the morning of 1st October she was awakened by severe abdominal pain, accompanied by sickness; as the patient appeared to be seriously ill she was sent into a nursing home. At the time of admission there was no oedema, no temperature, her pulse was only 88, and apart from her pallor, there were none of the usual signs of haemorrhage present. About 8 oz. of darkly stained urine were drawn off, which on testing proved to be practically solid with albumen. A diagnosis of impending eclampsia was made and palliative/

* Dr Fordyce asked me to assist him at operation in this case and I have to thank him for permission to include it in this series. The case was published in the Edin. Med. Journ. N.S. XXX. 3. p.29.

(Erratum. This Case should have been included in Group II)

palliative treatment adopted. Some hours later a brownish haemorrhagic vaginal discharge appeared, the patient's condition rapidly deteriorated, a diagnosis of concealed accidental haemorrhage was made and laparotomy decided upon.

On opening the abdomen there was found a considerable quantity of blood-stained serum in the peritoneal cavity. The uterus presented the appearances characteristic of a concealed haemorrhage. It was of a bluish or purplish colour, not unlike that of an ovarian cyst with twisted pedicle, with numerous haemorrhagic patches in its less deeply coloured parts. On the right side this haemorrhagic discoloration was most marked, and there was a large haematoma in the right broad ligament, which seemed to extend sub-peritoneally deeply into the pelvis.

A supravaginal hysterectomy was performed without opening into the uterus at all.

After a temporary recovery the patient died six weeks following operation from thrombosis of the pulmonary artery.

Pathological report. Uterus: There was a diffuse congestion and discoloration over the whole surface, giving the uterus an appearance not unlike that of a twisted ovarian tumour, and in the cornual regions there was actual extravasation of blood under the peritoneal coat. There was no fissuring of the peritoneum./

peritoneum. The whole uterus was hardened with the foetus in situ and later opened by a mesial incision; almost the whole of the placenta had been detached by haemorrhage, some of the blood clot behind it being recent, most of it older. On microscopic examination the separated portion of the placenta shows the signs of infarction - crowding and congestion of the villi and coagulation in the intervillous spaces. Sections through the uterine wall show very characteristic changes. In many areas the whole muscular structure of the wall is ploughed up by the escape of blood from the vessel. There are large haemorrhages separating the muscle bundles in some areas, while in others the haemorrhages are smaller and have caused separation of the individual muscle fibres. In these areas there is considerable degeneration of the muscle fibres, varying in degree, but showing itself for the most part in the loss of nuclear staining. Here and there there is some fragmentation of the muscle fibres, which have a clear hyaline appearance. In some sections there is distinct evidence of a minor degree of leucocytic infiltration and of degenerative changes in the decidua.

The destructive and degenerative changes in the uterine wall are naturally most marked in the neighbourhood of the placental site, but are not restricted to it. Sections taken through the wall of the uterus

on/

on the opposite side also show haemorrhages into the muscular substance and some degree of muscular degeneration.

GROUP II.

Cases of Accidental Haemorrhage with albuminuria on admission but with no toxaemic symptoms preceding the bleeding (exclusive of cases of eclampsia): eight cases.

Case 7. J.W. aet. 26 years. Primigravida.

Previous History: Six years ago the patient was confined to bed for three weeks with measles, this was followed by marked anaemia. One year ago she was an in-patient for one week in the Royal Infirmary with mild septicaemia following a whitlow; this was again followed by severe anaemia and almost complete amenorrhoea.

History of present pregnancy: L.M.P. 11th September 1919. There was nothing of note till the occurrence without warning of a fairly severe vaginal haemorrhage on the 24th May 1920 about 11 a.m., for which she was admitted to the Royal Maternity Hospital. On admission the patient was rather collapsed and complained of thirst, headache, and abdominal discomfort; labour had not commenced. No further bleeding occurred and the patient was delivered of a living male child on the 26th May at 4.45 p.m., the placenta being expressed half-an-hour later.

Urine./

Urine on admission. Albumen in considerable amount present.

26.5.20. Albumen still present.

30.5.20. Urine almost clear.

Placenta. The maternal surface of the organ is covered over a large area by a black jelly-like clot fairly firmly adherent. The remainder of the placenta appears normal except in one localised portion where an area of solidification can be palpated. On cut-section three distinct appearances are observed:- a large proportion of the placenta is normal; subjacent to the clot, however, the tissue is compressed and congested, i.e. in the condition of early infarction; in close proximity to this is a patch of solidification, pale pink in colour, irregular in outline and almost the size of a walnut - an old infarct. Underneath these infarcted areas is a zone of healthy placental tissue.

Microscopic Section:- cut so as to include all three areas.

In one portion of the section the placenta is normal in appearance; in another area (towards one end of the slide) the early stage of infarction may be observed; an extreme degree of congestion of the vessels of the villi is present, the stroma in places being almost completely obliterated; the villi are more closely crowded together than normal, and some proliferation/

proliferation of the syncytial nuclei is observed, more especially towards the decidual aspect; in places an intervillous coagulum is seen (see microphotograph No.6). In an adjacent part of the section a more advanced stage in the process of infarction is seen. Epithelial degeneration is marked and loss of nuclear staining is almost complete. The blood in the villi and the coagulum in the intervillous spaces has almost entirely disappeared. In places the villi appear to have fused, their outlines showing as masses of homogeneous tissue staining deeply with eosin.

Case 8. Mrs K. aet. 42 years. XVIII-para.

Previous History: The patient's general health has been good; the previous pregnancies and labours have been uncomplicated.

History of present pregnancy: L.M.P. 15th September 1919. Except that the patient has suffered from varicose veins, her general health during pregnancy has been good. On the 28th May 1920, she did a heavy washing and in the evening was seized with severe bearing down pain on each side of the abdomen. This disappeared during the night. On the following afternoon she was very drunk and was found by her husband about 4 p.m. semi-conscious, lying in a pool of/

of blood. She was admitted 6 p.m. to the Royal Maternity Hospital in a collapsed condition; vaginal bleeding was still going on in moderate amount; the os admitted three fingers. The patient was delivered at 1.35 a.m. on the 30th May of a still-born female child, the placenta being born immediately afterwards. Puerperium uneventful.

Urine. At time of admission - trace of albumen present.
30.5.23. Considerable deposit of albumen.
5.6.23. Urine clear.

Placenta. About one-and-a-half pints of fresh blood clot, slightly adherent, cover approximately one half of the maternal surface. Cut-section of placenta held under running water shows that portion of the organ underlying the clot to be intensely congested, though apparently normal in consistence. In this case the area of congestion is not, as usual, sharply defined, but merges gradually and in streaky fashion into the adjacent parts.

Microscopic Section:- Taken through an area of placenta where a congested streak runs into a paler portion. Towards one end of the slide normal placental tissue is seen, this gradually merging into an area where the villi are rather more congested and more closely packed together; in places blood clot is seen in the intervillous spaces; the appearances are possibly those of infarction in its earliest stages, but are not characteristic.

Case 9. Mrs F. aet. 34 years. IX-para.

Previous History: General health has always been good. Pregnancies and labours have all been normal with the exception of the fifth labour, which was complicated by severe post-partum haemorrhage.

History of present pregnancy: L.M.P. 24th November 1919. The patient has been doing heavy work and has felt weak and out of sorts from the commencement of pregnancy. For a few days prior to admission she noticed swelling of the feet and ankles, but there were no general symptoms. On the day of admission the patient did a heavy washing, after which she felt weak and exhausted and had some abdominal pain. Shortly after going to bed on the 29th July 1920 there was, about 9 p.m., a severe flooding for which she was admitted to the Royal Maternity Hospital at 11.15 a.m. A still-born child was delivered about three hours after admission; the placenta was born spontaneously immediately after the expulsion of the child. The puerperium was complicated by the development of phlegmasia alba dolens.

Urine: According to the patient's doctor the urine was albumen-free a few days before admission.

On admission. Albumen present (.6 grm. per litre).
30.7.20. Only a minute trace present.
2.8.20. Urine clear.

Placenta:/

Placenta: About one pint of loosely adherent blood-clot was scattered over the maternal surface. The placenta seems of normal consistence throughout, but on cutting longitudinal sections and washing, a very definite mottling is present, the normal placenta appearing bleached and contrasting with areas of congestion; these latter are specially noticeable in those portions of placenta underlying the site of clots on the maternal surface (see plate 8). It is probable from the appearance of those infarcted areas that internal haemorrhage had been going on for some hours before the occurrence of external bleeding.

Microscopic Section: Taken through congested area underlying clot. The placental tissue is in the condition of fairly recent infarction. Widespread clotting of blood in the intervillous spaces has occurred. In places the villi are closely packed together, in other areas they are widely separated by clot. Epithelial changes are not pronounced, although in places the formation of dark blue granular masses or buds, i.e. proliferation of the syncytial nuclei, is evident. From the history, the process is probably about twelve hours old.

Case 10. Mrs W. aet. 36 years. 11-para.

Previous History: The patient's general health has always been good; both previous pregnancies and labours have been normal.

History of present pregnancy: L.M.P. 6th June 1920. In the earlier months vomiting was rather excessive and she occasionally suffered from headaches. On the evening of the 8th January 1921 the patient was badly frightened by a pot of fat catching fire, and afterwards felt weak and shaky, though she was all right next day. At 10 a.m. on the 10th January a sudden severe vaginal haemorrhage occurred without apparent cause; the patient states that she lost about a pint of blood. She was admitted to the Royal Maternity Hospital at 6 p.m. on the same day, with oozing still going on from the vagina; the os admitted two fingers on admission. At 12.55 p.m. on 11th January a slightly macerated male foetus was delivered. Puerperium uneventful.

Urine: On admission heavily loaded with albumen.

17.1.21. Albumen still present in considerable amount.

25.1.21. Urine almost clear.

Placenta: About one-and-a-half pints of black blood-clot were loosely attached to the maternal surface. On section the placenta is extensively/

extensively disintegrated, being deeply and irregularly eroded by blood-clot which in some places appears to have eaten right through almost to foetal surface. Subtending the clots the tissue shows marked congestion and is of a consistence firmer than normal. Only in a few places does the placental tissue appear normal.

Microscopic Sections:- No.1. Taken through area underlying recent clot. The section shows the clot and subtending it an area of infarction, probably of two or three days standing. The villous vessels are greatly distended and in places appear to have ruptured; the villi themselves are in places somewhat crowded together, in other places they are separated from one another by a dense, fairly fresh coagulum. The villous epithelium is swollen and the nuclei are stained more deeply than normal, showing that the process is still in a recent phase. The characteristic features of infarction become less definite the further one passes in the direction of the foetal surface, i.e. away from the clot responsible for its development.

No.2. Taken through a portion of placenta underlying fairly old blood-clot. This section shows placental tissue for the most part normal in appearance. At one corner, however,/

however, a small retro-placental clot is seen, and in immediate relation to it is a small circumscribed area of old infarction. The villi are rather club-shaped and coarser than normal. Note also that in places the villous vessels seem to have disappeared, although those still remaining are more congested than usual. The stroma of the villi is unusually dense and the cells seem rounder and less spindle-shaped than normal; probably syphilitic.

Case 11. Mrs T. aet. 37 years. XI-para.

Previous History: General health always good. Has had twins twice, otherwise obstetric history is normal.

History of present pregnancy: L.M.P. 12th November 1919. Pregnancy was uneventful till the afternoon of the 7th May 1920 when, without obvious exciting cause, the patient lost about one pint of blood per vaginam. Oozing continued till she was admitted to the Royal Maternity Hospital on the 10th May; the patient was not in labour, the haemorrhage ceased spontaneously, and after being kept under observation for three days she was discharged on the 13th May. No further bleeding occurred, but labour commenced on the 18th May for which patient was re-admitted, and was delivered on the same evening of twins, one of which was still born. Puerperium/

Puerperium uneventful.

Urine: 10.5.20. A trace of albumen present.
14.5.20. A trace of albumen still present.
18.5.20. Urine clear.

Placentae. No. 1. Normal in appearance. On section nothing abnormal is observed except that the organ is rather paler than usual.

No. 2. The maternal surface is covered by one large clot, black and jelly-like and fairly firmly adherent. On section, the clot has a layered appearance suggesting the occurrence of smaller preceding haemorrhages; the placental substance is deeply eaten into and the tissue underlying the clot is deep purple in colour and of a consistence much firmer than normal. In other parts one or two old irregular infarcts are seen.

Microscopic sections: No. 1. Taken through centre of apparently healthy placenta. The tissue appears normal; note absence of inter-villous coagulum, of villous congestion, or of epithelial disintegration.

No. 2. Taken through area of placenta underlying clot. The section is of interest in that it shows different stages in the process of infarction. In one area the changes are more or less recent, and consist in a crowding together of the villi, a moderate degree/

degree of congestion in the villous blood-vessels, and in the presence of a coagulum in the intervillous spaces. In places loss of nuclear staining in the epithelium has occurred. In another portion of the section the changes are more advanced; the intervillous coagulum is of older standing, and degenerative changes in the epithelium are more marked, nuclear staining being almost entirely lost; the villi are closely packed together and in places neighbouring villi have become fused.

Case 12. Mrs F. aet. 27 years. 1-para.

Previous History: There is nothing to note. The previous pregnancy and labour were normal.

History of present pregnancy: L.M.P. 10th January 1920. The patient's general health during pregnancy has been excellent. On the afternoon of the 2nd August 1920 the patient was greatly frightened by a thunder storm and had to lie down. Foetal movements are said to have ceased a few hours later. During the night severe abdominal pain was complained of. At 8 a.m. on the 3rd August a free external haemorrhage occurred. During the forenoon the patient suffered from thirst and headache. She was admitted to the Royal Maternity Hospital about 1 p.m. on the same day and appeared very ill; pulse 110; blood pressure/

pressure 160 mm. Hg. At 2.10 p.m. a still-born foetus was expelled, the placenta being born immediately afterwards.

Urine:- On admission almost solid with albumen.

6.8.23. Still a considerable deposit of albumen present.

14.8.23. Urine practically clear.

Placenta: The maternal surface is irregularly covered with a pint or so of firm blackish clot; on attempting to remove the clot, some remains firmly adherent. On cut-section the clot is seen to have deeply eroded the placental tissue. The surface of the placenta appears mottled; almost one half of the organ is in the condition of early infarction, although only in a few places is there definite solidification. The congested areas fairly accurately subtend the site of clots on the maternal surface. The presumably healthy placental tissue is rather paler than normal.

Case 13. Mrs M. aet. 28 years. IV-para.

Previous History: The patient has always been rather anaemic, otherwise there is nothing to note. The previous pregnancies and labours have all been normal, with the exception of the first pregnancy which was complicated by albuminuria.

History/

History of present pregnancy: L.M.P. uncertain. Quickening early in February 1921. The patient's health during pregnancy up till about end of the seventh month was good. On the 5th of June a slight haemorrhage occurred and passed off. During the ninth month the patient has been feeling rather run down and easily tired, but there have been no definite toxic symptoms. On the 20th June, in the forenoon, there was a fairly sharp vaginal haemorrhage; this was followed by the onset of labour pains; she was delivered of a living male child at 10 p.m. on the same day, the placenta being spontaneously expelled a few minutes later.

Urine:- About the thirty-fifth week, albumen appeared in the urine and persisted till term.

21.6.21. Trace of albumen present.

25.6.21. Urine clear.

Placenta: The placenta is thinned out and pale. A considerable amount of fairly fresh blood clot irregularly covers the maternal surface. In two places, each about the size of a crown piece, old organised clot is present and firmly adherent to the placenta, one clot appearing to be of older standing than the other. On cutting sections of the placenta longitudinally through these areas, the tissue subjacent to each is seen to be infarcted; that/

that underlying the fresh blood clot is deep purple in colour, but of normal consistence; under the more recent of the two older clots the placenta is brick-red and firm; under the oldest clot the tissue is yellowish in colour and cheesy in consistence, i.e. in the condition of white infarction.

Microscopic sections No. 1. Taken through the most recent area of infarction. In one portion of the section normal placental tissue is seen, the villi being at a normal distance from one another, not congested, and showing no sign of degeneration in the epithelial structures; the inter-villous spaces are quite free from blood-clot. Sharply defined from this is a second area in which the appearances of well established infarction are evident: the villi are closely crowded together and in places neighbouring villi have become fused by masses of fibrin; a marked degree of congestion of the villous vessels is present; epithelial degeneration as shown by loss of nuclear staining is noted.

No. 2. Through a less recent area of infarction. In this section a certain proportion of normal tissue is seen, and sharply defined from it an area of infarction in its more advanced phase. Fusion of the villi is widespread and disintegration of epithelium well marked, nuclear staining in the syncytial layer being almost or entirely lost. The blood-clot in the villous/

villous vessels and intervillous spaces is of old standing, the blood corpuscles being pale in colour, and in many places being represented by shadowy outlines. Degenerative changes in the stroma may also be noted. In one localised area the changes appear to be of more recent development.

No. 3. Through an old whitish infarct. A narrow margin of normal placental tissue has been included for purposes of comparison; the area of infarction is sharply defined from it. The appearances are those of infarction in its ultimate stages. Epithelial degeneration is now complete, with rare exceptions, all trace of nuclear staining being lost. Fusion of the villi is widespread, giving the whole a homogenous fibrous appearance, staining deeply with eosin. In many places no trace of the villous vessels has remained; in a few instances the vessels are still distinct, the coagulum in their interior however has almost entirely disappeared.

GROUP III.

Cases of Accidental Haemorrhage in which the urine was clear on admission, but in which albumen was subsequently present: Two cases.

Case 14. Mrs H. aet. 31 years. 11-para.

Previous History: General health, with the exception of measles and whooping cough in childhood, has always been good. Both previous pregnancies and labours were normal.

History of present pregnancy: L.M.P. 10th January 1919. Except that patient has felt weak and run down during the last six weeks, the pregnancy has run a normal course. The patient was admitted to the Royal Maternity Hospital 2.30 p.m. on 2nd August 1920 with the history of a severe vaginal haemorrhage having occurred at 9 a.m. on the day of admission. On admission the patient complained of constant pain over the abdomen and across the sacrum; the uterus was rather tense, and there was an area of tenderness over the lower left quadrant of the abdomen. Pulse 115; Temperature 98.4°F.; blood-pressure 135 mm. Hg. The patient was delivered of a living child at 6 p.m. on the day of admission.

Urine:/

Urine: 3 p.m. 2.8.20. No albumen present.
6 p.m. 2.8.20. No albumen present.
10 a.m. 3.8.20. Considerable deposit of albumen present.
6.8.20. Urine clear.

Placenta. About one pint of fairly fresh blood-clot was expelled with the placenta. On cut-section, the main mass of the placenta is much paler than normal. About the centre of the placenta is a saucer-shaped depression, about four inches in diameter, apparently compressed by blood-clot. The placental tissue underlying this is normal in consistence but is deep purple in colour, contrasting very strikingly with the paler adjacent tissue.

A microscopic section taken through the congested portion showed this part to be in the condition of early infarction, the villous vessels being definitely congested and the villi closely packed together. In places a fine coagulum occupies the intervillous space.

Case 15. Mrs W. aet. 36 years. VIII-para.

Previous History: Health has always been poor. The second pregnancy was complicated by eclampsia, although a living child was born. In the fifth and/

and seventh pregnancies there was albuminuria.

History of present pregnancy: L.M.P. and date of "quickening" both uncertain. The patient has not felt well since the early months of pregnancy, although there have been no symptoms of toxaemia and the urine has remained clear. On the morning of the 3rd July 1921 a slight haemorrhage occurred and ceased spontaneously; on the following day about 10 a.m. the haemorrhage recurred, a considerable quantity of blood, estimated by the patient at about a pint, being lost. The patient was delivered at 8 p.m. on the 4th July of a still-born child.

Urine:- At time of delivery no albumen present.

5.7.21. Albumen definitely present.

(No further examination of the urine was made)

Puerperium uneventful.

Placenta: Some blackish blood clot was loosely and irregularly adherent to the maternal surface. On cut-section, about one half of the organ appears normal; there are no areas of obvious infarction, - but a large proportion of the placenta is of a deep purple colour, the congested area being fairly sharply defined from the paler adjoining tissue; it probably represents the process of infarction in its earliest stages.

GROUP IV.

Accidental Haemorrhage combined with eclampsia: Five cases.

Case 16.* Mrs W.R. Primigravida.

Confinement expected on July 16th 1920.

Urine examined at intervals of three weeks from April onwards. No abnormalities detected. Dr Hill Buchan was called in late on the evening of June 17th on account of a "breathless attack". He found the patient sitting up in bed in distress. Physical examination of the chest proved negative. There was some oedema of the legs, and she complained of constant pain in the abdomen. The uterus was tender on palpation and felt hard and tense. Before the doctor's arrival there had been no external haemorrhage, but it began a few minutes afterwards. It was not at all profuse, but the patient felt considerably relieved after it had occurred, and the uterus felt distinctly less tense. No foetal heart sounds were audible. Vaginal examination was negative. Immediate removal to hospital was arranged. In the cab the patient's/

* This case which was reported by Drs Fordyce and Johnstone in the Proceedings of the Royal Society of Medicine, Section of Obstetrics and Gynecology Vol.XIV. No.5. p.244, occurred in the Royal Maternity Hospital while I was Dr Fordyce's house-surgeon, and I have to thank him for permission to include it in this series.

patient's pulse, which was rather poor to begin with, became worse, and she became breathless again, and complained of great thirst. Before the evening of June 17th the patient had been able to carry out her ordinary household duties without complaint, but for the two days immediately preceding the attack she had not felt quite so well.

State on admission: The patient was somewhat collapsed as the result of a fairly severe haemorrhage, and as no placenta could be felt, the diagnosis of accidental haemorrhage was made. There was considerable oedema of the trunk and lower limbs; and the urine was scanty and contained a large quantity of albumen. As the condition of the pulse did not indicate any immediate danger, it was decided to allow the patient to rally before undertaking any treatment. As the morning progressed, however, the pulse-rate became increasingly rapid, although there was no further vaginal haemorrhage. The uterus also became gradually larger and harder. Toxic symptoms now began to manifest themselves in a dimness of vision, sickness, and a slowly increasing tendency to coma. By the early afternoon she had complete suppression of urine, and had shown several twitchings of the face, but had not had any actual fit. The diagnosis of concealed accidental haemorrhage/

haemorrhage with progressive toxaemia was made, and as the cervix was quite closed and rigid, Caesarean section was determined upon.

The operation: Under anaesthesia induced with chloroform and maintained with open ether, the abdomen was opened by a mesial incision. The condition of the uterus at once attracted attention. The upper part of the anterior wall appeared deeply congested and haemorrhagic. This was most marked in the region of the right cornu, where the wall presented a deep purple or black appearance evidently due to haemorrhage. The same appearances were present in the adjacent broad ligament and proximal half of the Fallopian tube. It was remarked at the time that the appearances suggested some interference with the right ovarian vein, associated with "backward pressure" and haemorrhage. There was a small patch of subperitoneal haemorrhage just below the left cornual region, but otherwise the left side of the uterus was paler and more normal in appearance. On opening the uterus by the usual mesial incision it was noted that the uterine wall was deeply infiltrated with extravasated blood of a dark colour. The placenta lay on the posterior and right lateral walls. It was separated from the right lateral wall by a large retroplacental clot, whilst its left half was/

was still attached to the posterior uterine wall. The child was immediately extracted, and, although dead, it showed no evidence of maceration. The placenta was then detached manually. At this stage it was decided that the condition of the uterus was such as to make its removal desirable. Supravaginal hysterectomy was accordingly carried out. The abdomen was closed as rapidly as possible and the patient returned to bed. Intravenous saline transfusion was performed during the closing stages of the operation, but the patient's condition rapidly became worse and she died four hours later.

Pathological description:-

Uterus: The external appearance of the anterior wall has already been described. The posterior showed similar changes. At no point was there any fissuring of the peritoneum (see Plate 2). A horizontal section made just below the orifices of the tubes showed extensive haemorrhages in the muscular wall of the right half of the uterus. The left half was similarly involved but to a much less extent. Over the area corresponding to the deepest superficial coloration the haemorrhage was most evident towards the peritoneal aspect. The decidua showed no evident changes.

Microscopically/

Microscopically the muscular wall in the affected areas was ploughed up by haemorrhage, the muscular fibres showing all stages of degeneration. In the non-haemorrhagic regions the muscular fibres were healthy. There was thrombosis in the veins of the uterine wall.

Placenta: In the fresh state the placenta showed attached blood clot over the separated area - roughly about a third of the total placenta. The remainder of the decidual surface was normal except for a small clot attached along the margin. Even to the naked eye there was an evident differentiation of the placenta into two areas. The area of separation had a deep purple colour whilst the remainder was paler. On section in the fresh state the line of demarcation between these two areas was clearly marked. After hardening in formalin for one night the appearance shown in the plate was present (see Plate III). The differentiation was still more evident and two other areas of infarction, one recent, the other old, were noted in the attached portion, and one old and pale infarct at the margin of the separated part.

Microscopically the separated area of placenta showed the signs of early infarction - namely, coagulation/

coagulation in the intervillous spaces and congestion and crowding of the villi.

A full post-mortem was refused, but permission was given for the abdomen to be reopened. The liver and kidneys were accordingly removed.

Liver: This showed multiple subcapsular haemorrhages and its surface was pale and fatty. On section the appearances typical of eclampsia were present, namely, extensive haemorrhages and fatty and necrotic changes. (see Plate IV)

Kidneys: The cortex was thickened and fatty, with multiple small areas of more marked degeneration.

Case 17. Mrs Y. aet. 28 years. 1-para.

Previous History: General health always good. The first pregnancy terminated in a miscarriage at five-and-a-half months.

History of present pregnancy: L.M.P. 28th December 1919. Patient's health during the earlier months of pregnancy was excellent; up till the time that consciousness was lost, no symptoms of any kind were complained of; the urine was tested repeatedly with negative results, the last analysis being made ten days before the first eclamptic convulsion occurred./

occurred. The patient was admitted to the Royal Maternity Hospital at 10 a.m. on July 21st 1920, with the history that two fits had occurred some hours previously; on admission the patient was moderately deeply comatosed; labour had not commenced. The blood pressure was 210 mm. Hg.; the urine became solid with albumen on boiling. Treatment along the usual conservative lines was carried out, and at 6 a.m. on July 26th a slightly macerated child was born. During a lucid interval on July 23rd the patient stated that she still felt foetal movements. From its appearance at birth the child had probably been dead about two days.

Puerperium. Recovery was slow, albumen still being present in small amount ten days after delivery.

Placenta: (see Plate V)

The placenta is very irregular in shape and consistence, some parts being soft, others firm and liver-like. Almost one half of the maternal surface is covered with loosely adherent blackish blood-clot, on the removal of which the subjacent tissue, while not depressed appears congested and of much firmer consistence than normal. Over one localised area, in extent about that of a crown piece, firm adherent black clot is present. On cutting sections of the placenta the tissue underlying/

underlying the clots is seen to be markedly congested and firmer in texture than normal, i.e. in the condition of infarction; almost one half of the placenta appears to be diseased. One or two old small whitish areas of infarction are present.

Microscopic section: Taken through an area of solidification under the older clot (see microphotograph No.12).

The appearances here are those of infarction in its less recent stages; the villi are more closely crowded together than normal, and while here and there are separated by an intervillous coagulum of old standing, in many places the villi appeared to be fused together by fibrin; epithelial disintegration is marked and is shown at this stage by loss of nuclear staining. Degenerative changes, probably of the nature of a coagulation necrosis, are also to be found in the stroma cells.

Case 18. Mrs T. aet. 38 years. Primigravida.

Previous History: Patient's general health has always been good.

History of present pregnancy: L.M.P. 15th March 1920. During the earlier months of pregnancy there were no untoward symptoms. For two or three weeks/

weeks before admission, occasional headaches and some oedema of the lower limbs were complained of. About ten days before admission severe headaches, eye symptoms, and widespread oedema suddenly developed, these being associated with attacks of severe pain felt diffusely over the abdomen. The patient was confined to bed for about a week prior to admission. At 5 p.m. on the 28th November 1920 the patient was admitted to the Royal Maternity Hospital, with a history of five eclamptic seizures having occurred since 4 a.m. on the same day. The blood-pressure was 225 mm. Hg., and the patient was profoundly comatose. At 10 p.m. on the day of admission, a still-born child was delivered. Recovery uneventful.

Urine: Solid with albumen on admission.

10.12.20. Urine clear.

Placenta: (see plate VI)

The maternal surface of the placenta is irregularly covered with dark, adherent clots over two-thirds of its area. Under these the placenta appears to be depressed and of a firm consistence. On cut-section the organ is seen to be considerably broken up by blood-clot, and extensively infarcted. Under a more or less recent area of clot, the features of infarction in its earlier stages are observed;/

observed; the tissue is deep red in colour, and the normal spongy texture of the placenta is lost. In other parts of the placenta more advanced stages of infarction are found; many of these subtend blood cysts in the substance of the organ, one such being depicted in plate VI. A few old white infarcts are also present.

Microscopic section:- Taken through an area of placenta underlying a blood cyst. The appearances are those of a moderately recent infarction, the process being apparently furthest advanced towards the centre of the section, where there is evidence of degeneration of epithelium in loss of nuclear staining, partial or complete. In places the haemoglobin has been dissolved out of the blood clot in the villi and intervillous spaces. In many places patches of necrotic decidua are seen; (this last is of course not an abnormal finding).

Case 19. Mrs M. aet. 35 years. IV-para.

Previous History: General health has always been good. The first and second pregnancies and labours were normal, the third and fourth pregnancies terminated prematurely at the end of the eighth month, a still-born child being delivered in each case;

(cause/

(cause of premature labour unknown).

History of present pregnancy: L.M.P. 5th December 1919. Patient's health during the earlier months of pregnancy was satisfactory. About the 10th of July 1920 symptoms of toxaemia appeared and developed very rapidly, frontal headache being severe and abdominal pain acute. The patient was admitted at 2 a.m. on the 17th July with a history of three eclamptic convulsions and some vaginal haemorrhage having occurred; blood-pressure 180 mm. Hg.; she was delivered by version of a still-born premature child seven hours after admission. Immediately after the birth of the child the placenta was spontaneously expelled along with a large quantity of blackish blood clot. No further seizures occurred after delivery. On the seventh day of the puerperium the urine was practically free of albumen.

Placenta: (see Plate VII)

About one-and-a-half pints of loose black clot came away with the placenta at birth. Some older clot, fairly firmly adherent is irregularly scattered over the maternal surface. Near the margin of the placenta at one part is a cup-shaped depression the size of a walnut, occupied by old blood clot. The consistence of the placenta is irregular, localised firm areas being scattered throughout the substance/

substance of the organ. On section the placenta is seen to be extensively diseased, the greater part being intensely congested and of a consistence rather less spongy than normal, the condition being one of recent infarction. Under a circumscribed area of old adherent organised blood clot is a zone of older infarction brick-red in colour. A few old white infarcts are also present; in the centre of one of these liquefaction has occurred.

Case 20. Mrs S. aet. 39 years. IV-para.

Previous History: No previous illnesses. Previous pregnancies and labours all normal.

History of present pregnancy: L.M.P. 15th August 1919. Pregnancy ran a normal course till about the second week of April, when, in the evening, after a day's heavy washing, the patient was seized suddenly with severe griping pain low down in the abdomen and felt faint; there was no external bleeding, and foetal movements were not interfered with. The pain was present in a mild degree for a week or so. On the afternoon of the 21st April a severe vaginal haemorrhage occurred, about a pint of blood being lost. The patient was admitted to the Royal Maternity Hospital at 3.20 a.m. on the 22nd April 1920 with the/

the history that one fit had occurred one hour previously. On admission, the patient was losing blood freely per vaginam, she was extremely collapsed, the pulse being almost imperceptible; the os was three-quarters dilated. The urine was loaded with albumen. A second convulsion occurred at 3.40 a.m. At 5.45 a.m. on the same morning a still-born child was delivered, followed immediately by the placenta and a large quantity of blood-clot. No further seizures occurred. Recovery was slow, but after three weeks the patient was discharged well, the urine being free from albumen.

Placenta: A large blackish clot is loosely adherent to the maternal surface. On cutting longitudinal sections the area underlying the clot is much depressed, and in places is deeply eaten into. The placenta has a mottled appearance, areas of deep congestion alternating with parts which seem abnormally anaemic. Under the depression in the centre of the organ the tissue is dark purple in appearance and liver-like in consistence. One or two old white infarcts are irregularly scattered throughout the placenta.

GROUP V.

Cases of Accidental Haemorrhage in which the urine remained albumen-free throughout: Five cases.

Case 21. Mrs T. aet. 36 years. IX-para.

Previous History: The patient has been in poor health for five or six years; there have been no definite symptoms, but she has been very easily tired, and is breathless on slight exertion. A pre-systolic bruit in the mitral area is present.

History of present pregnancy: L.M.P. 12th January 1920. Vomiting has been a more or less constant complaint, and from the early months of pregnancy the patient has felt weak and ill. About 2 p.m. on the day before admission, she states that while washing clothes she slipped and struck her abdomen against the washing-board. Shortly afterwards oozing of blood commenced from the vagina and continued till admission. The patient was admitted to the Royal Maternity Hospital on 4th September at 6 a.m., in a collapsed condition. Labour was in progress and spontaneous delivery of a living child occurred at 10.30 a.m. Puerperium uneventful.

Urine: Examined on the day of admission and at daily intervals thereafter for four days; analysis negative on each occasion.

Placenta: The placenta is very large and irregular in shape, and of marked pallor. No areas of abnormal consistence are detected. A small amount of blood clot is irregularly scattered over the maternal surface. On section, except that the organ appears unusually anaemic, very little abnormal is found. Towards the edge of the placenta at one part a small circumscribed area of recent infarction is present.

Microscopic section: Taken through the infarcted area. Towards the decidual surface in one localised area there is a small portion of placenta having the appearances of very early infarction; the remainder of the tissue is normal. (an unsatisfactory section).

Case 22. Mrs R. aet. 40 years. VI-para.

Previous History: Patient's general health has always been good; obstetrical history normal.

History of present pregnancy: L.M.P. June 1921; quickening about the end of October 1921. The patient's health was apparently perfect till about 1.30 p.m. on the 13th January 1922 when without warning or obvious exciting cause, there was a copious vaginal haemorrhage,/

haemorrhage, the amount lost being estimated at about a pint and a half. Oozing of blood from the vagina continued until the patient was admitted to the Royal Maternity Hospital at 6 p.m. on the same day. On admission the patient was intensely anaemic, the pulse being almost imperceptible; the os admitted two fingers; membranes were intact. Dilatation of the cervix was completed by a Champetier de Ribes' bag, and labour terminated spontaneously nine hours after admission. The placenta was removed manually. Puerperium uneventful.

The urine tested at daily intervals remained free from albumen throughout.

Placenta: Some dark firm clot is loosely adherent to the maternal surface. No areas of abnormal consistence can be detected on palpation. Longitudinal sections of the placenta held under running water shows an irregular mottling, the tissue being on the whole paler than normal. No areas of recent infarction are to be found, although one or two old infarcts, the largest about the size of a hazel-nut, are present.

Case 23. Mrs C. aet. 38 years. IX-para.

Previous History:- With the exception of the fevers of childhood, the patient's general health has always been good.

History of present pregnancy: L.M.P. 7th May 1921. During the earlier months of pregnancy sickness was excessive and from the time of conception the patient has never felt really well. About 3 o'clock on the afternoon of the 21st February 1922 a free vaginal haemorrhage occurred, about a pint of blood being lost; this was accompanied by severe griping pain over the lower part of the abdomen on both sides. The patient was admitted to the Royal Maternity Hospital at 5.45 p.m. on the 21st February in a collapsed condition. Labour was then in progress, the os being almost fully dilated. The head was presenting and labour was terminated by forceps half an hour after admission. The child was still-born; no sign of maceration was present. The placenta was spontaneously expelled along with a soup-plateful of fairly fresh clot almost immediately after the birth of the child. The puerperium was uneventful.

The urine remained albumen-free throughout.

Placenta:- A few tags of dark clot are adherent to the maternal surface, especially towards the lower margin of the placenta. The consistence/

consistence of the organ except in one small localised area, appears uniformly soft and spongy. Longitudinal cut-sections of the placenta held under running water show nothing abnormal except that the tissue is rather more congested than usual; one small old white infarct is present.

Case 24. Mrs McK. aet. 41 years. XII-para.

Previous History: There is nothing to note as regards the patient's general health except that she has for some years been subject to attacks of bronchitis. The patient had eclampsia at the time of her first labour. The subsequent pregnancies and labours have all been normal.

History of present pregnancy: L.M.P. 20th June 1921. Health throughout this pregnancy has been poor, patient has felt weak and ill and has been unable to carry out her household duties. At 3 p.m. on the afternoon of the 1st March 1922 a considerable vaginal haemorrhage occurred, the amount of blood lost being estimated at about a pint. On admission to the Royal Maternity Hospital at 7 p.m. on the same day oozing of blood from the vagina was still going on. The patient was profoundly collapsed, very breathless, and almost blind. Labour was in progress, the os being almost fully dilated, the membranes still intact.

The/

The membranes were ruptured immediately and forceps applied, delivery of a still-born child being completed about five hours after the first onset of haemorrhage. The placenta was spontaneously expelled a few minutes after the birth of the child. The puerperium was rather febrile, but the patient was discharged well three weeks after her confinement.

The urine was examined shortly after admission and once subsequently and was free from albumen on both occasions.

Placenta: Nothing abnormal was detected on surface inspection. On cut-section the placenta is paler than normal and three old localised areas of white infarction are present; nothing else abnormal found.

Case 25. Mrs H. aet. 41 years. IX-para.

Previous History: General health has always been good. Three labours have been complicated by malpresentations, and on two occasions the puerperium has been febrile; otherwise there is nothing to note.

History of present pregnancy: L.M.P. 15th June 1921. The patient's health during this pregnancy has been excellent. Without obvious exciting cause/

cause at 10 p.m. on the 12th March 1922 a moderate vaginal haemorrhage occurred, about half a pint of blood being lost; labour mains were felt immediately afterwards. On admission to the Royal Maternity Hospital at 12.30 a.m. on the 13th March considerable oozing of blood from the vagina was going on; the patient's condition, however, was good; pulse 96, of good tension. Spontaneous delivery of a living child was accomplished two hours after admission, the placenta being expelled along with a good deal of blood clot fifteen minutes later, i.e. about five hours after the onset of haemorrhage. The puerperium was uneventful.

The urine was tested shortly after admission and also on the two days following and on each occasion the examination was negative.

Placenta: Nothing abnormal detected either on surface inspection or on cut-section.

B. PLACENTA PRAEVIA.

The cases have been grouped as follows:-

1. Placenta Praevia with albuminuria on admission but with no toxaemic symptoms preceding the bledding (exclusive of cases of eclampsia): Seven cases.

2. Placenta Praevia in which the urine was clear on admission but in which albuminuria was subsequently present: One case.

3. Placenta Praevia combined with eclampsia: One case.

4. Placenta Praevia in which the urine remained albumen free throughout: Eight cases.

GROUP I.

Cases of Placenta Praevia with albuminuria on admission but with no toxaemic symptoms preceding the bleeding (exclusive of cases of eclampsia): Seven cases.

Case 26. Mrs McL. aet. 41 years. VII-para.

Previous History: General health has always been good; nothing of importance to note in obstetric history.

History of present pregnancy: L.M.P. 8th August 1920. The patient was admitted to the Royal Maternity Hospital on 10th May 1921, with a history of vaginal haemorrhage having occurred intermittently for a month previously. At 4 a.m. on the day of admission she wakened up with the bed clothes soaked with blood. On admission at 7 a.m. labour was in progress, the os being almost fully dilated; bleeding in considerable amount was still going on, and a diagnosis of central placenta praevia was made. Delivery by version of a still-born child was accomplished about three-quarters of an hour after admission. Recovery uneventful.

Urine: The urine was examined shortly after admission and contained a trace of albumen, on the following day a trace of albumen was/

was still present. Four days after delivery no albumen was present.

Placenta: The praevia portion of the placenta is rather broken up as the result of manipulations during delivery. Some tags of blood clot are adherent to the maternal surface in the neighbourhood of the lower placental margin. Cut-section of the placenta shows congestion of the separated portion, very definitely contrasting with the pallor of the main mass of the organ.

Microscopic section: Taken through praevia portion. (see microphotograph No.4). All the features of very definite infarction in its earliest stages are present. The villi are closely crowded together and their vessels are greatly congested. Early degenerative changes in the syncytium are evidenced by proliferation and unduly deep staining of the nuclei. In places a diffuse intervillous coagulum is noticed. These changes are more marked towards the maternal aspect; as the foetal surface is approached more or less normal placental tissue is found. Towards one end of the section, in a small localised area, the process of infarction is apparently further advanced; the blood corpuscles in the villi and intervillous spaces being paler in colour, and here/

here and there are represented merely by shadowy outlines. In this area, too, loss of nuclear staining, showing a more advanced stage of epithelial degeneration, is found.

Case 27. Mrs H. aet. 26 years. 1-para.

Previous History: General health has always been poor. A year ago the patient was treated as an in-patient in Leith hospital for "heart disease". The previous pregnancy and labour were normal.

History of present pregnancy: L.M.P. 10th October 1920. Beyond a feeling of weakness and being generally run down there was nothing of importance to note until a moderate vaginal haemorrhage occurred on the 16th March 1921, about half a pint of blood being lost at this time. On the 22nd March a second haemorrhage, rather more profuse than the first, occurred. Oozing of blood from the vagina continued till the 24th March when she was admitted to the Maternity Hospital. On admission the patient was not in labour. The vagina was packed and pituitrin was given. Labour pains commenced on the evening of the 25th March; a diagnosis of central placenta praevia was made; a still-born child was delivered by version at 12 noon on the following day.

On admission the patient was slightly jaundiced and the/

the urine contained a trace of albumen. During the early hours of the morning of the 27th March deep jaundice quickly developed and the amount of albumen rapidly increased; the urine contained no leucin, tyrosin, nor acetone bodies.

Later in the day the patient became stuperose, and early on the morning of the 29th coma supervened from which consciousness was not regained. Before death the spleen was found to be enlarged, the liver much diminished in size, and a leucocytosis of 60,000 was present. Permission for a post-mortem examination was refused.

Placenta: The placenta has been rather broken up by manipulations during delivery. In appearance and consistence the organ seems normal except for a firm congested area about the size of a crown piece close to the placental margin. On cut-section this area was found to be definitely congested and solidified, otherwise no abnormalities were detected.

Microscopic sections. No. 1. Taken from the centre of the "hepatised" area: The appearances are those of infarction probably about ten days old. Throughout almost the entire section the villi are greatly engorged, the blood-vessels being in some cases so congested that the stroma of the/

the vessels is compressed into a very thin layer under the epithelium. In some places there is evidence of rupture of the villous vessels with haemorrhage into the intervillous space. The villi are in many places closely packed together and here and there appear to be fused together by fibrin, in other places they are separated from one another by a diffuse flocculent coagulum. The blood clot is pale in colour, the haemoglobin being partially dissolved out. The villous epithelium shows a considerable degree of disintegration, in many places nuclear staining being lost.

No. 2. Taken through the margin of the more densely infarcted area, presumably through an area of more recent separation (see microphotograph No.5) The features of infarction are here less definite than in Section No.1, the process is probably more recent. The crowding together of villi is less dense, and epithelial degeneration as evidenced by loss of nuclear staining, while present, is less pronounced; the villous congestion is intense, and there is a considerable intervillous coagulation, the blood-clot, however, appears fresher than in the preceding section.

Case 28. Mrs M. aet. 46 years. VI-para.

Previous History: There is nothing of importance to note as regards the patient's general/

general health. The previous pregnancies and labours have been normal.

History of present pregnancy: L.M.P. 10th July 1920. The patient's health during pregnancy was good until the 30th April 1921 when oozing of blood from the vagina commenced. The bleeding although not copious was more or less continuous, and was accompanied by sacralgia. About thirty hours before admission to hospital a free vaginal haemorrhage occurred, well over a pint of blood being stated to have been lost. On admission to the Royal Maternity Hospital on 6th May 1921 the patient was extremely collapsed, the pulse being almost imperceptible. Labour was in progress, the os being almost fully dilated. A lateral placenta praevia was felt. Delivery was completed by version two hours after admission. During the earlier days of the puerperium headache and dimness of vision were complained of, though to what extent these may have been due to anaemia is uncertain.

Urine: The urine on admission boiled solid with albumen, and contained blood. (Unfortunately no further urinary analysis was made).

Placenta: The main mass of the placenta appear to be of normal colour and consistence, the praevia portion however is deeply congested; the margin of/

of the praevia portion is lighter in colour and much firmer in consistence than elsewhere. On section the contrast between the normal and the separated portions of the placenta is clearly defined. In the separated portion two types of infarction are obviously present: at the margin the process is further established and probably has resulted from separation a week or so prior to delivery; the larger more recent area of infarction has followed the separation causing the severe haemorrhage for which the patient was admitted.

Case 29.* Mrs B. XI-para.

Previous History: Health prior to admission to hospital had been perfect.

History of present pregnancy: Admitted to the Royal Maternity Hospital on the 18th July 1921, during the seventh month of pregnancy with a history of vaginal haemorrhage having occurred. A diagnosis of placenta praevia was made for which labour was induced./

* This case does not belong strictly to my consecutive series; I saw the patient for the first time in Ward 30 of the Royal Infirmary, and am indebted to Dr Chalmers Watson for permission to make this report. Unfortunately the notes taken during the patient's stay in the Maternity Hospital are somewhat incomplete; they are copied out here from the Special Case Book in the Maternity Hospital.

induced. Shortly after delivery violent headaches, vomiting, dimness of vision and widespread oedema developed; the urine was found to be heavily loaded with albumen, which was still present on discharge. The patient was admitted as a case of acute Bright's disease to the Royal Infirmary, and died of this condition in Ward 26 on the 2nd July 1922.

Case 30. Mrs B. aet. 32 years. VIII-para.

History of present pregnancy. L.M.P. 12th November 1919. Pregnancy was uneventful until the 23rd July 1920 when a moderately severe vaginal haemorrhage occurred. This ceased spontaneously, but at 2 p.m. on the 2nd August a second bleeding, more copious than the first occurred. Admitted to the Royal Maternity Hospital at 6 p.m. on the same afternoon. Labour was in progress and was completed by forceps at 1 a.m. on the following morning. Puerperium uneventful.

Urine: The urine had been tested at three-weekly intervals at the Cowgate Dispensary with negative results, the last examination having been made ten days prior to admission.

2.8.20. 7 p.m. Slight trace of albumen present.
3.8.20. 1 a.m. Abundant deposit of albumen present.
11.8.20. Urine albumen-free.

Placenta:/

Placenta: The organ is pale and of a normal consistence throughout, except for one small localised area of old white infarction, and except for the praevia portion which is deeply congested and firm to the touch. On cut-section the difference in appearance is well brought out; the congestion fades off as the main mass of the placenta is approached, suggesting that the blood poured out had forced its way upwards and separated the placenta higher up. The area of infarction, therefore, is not limited to, although most definite in the praevia portion.

Case 31. Mrs G., aet. 39 years. X-para.

Previous History: The patient has always enjoyed good health. There is nothing abnormal to note as regards her obstetrical history.

Present Pregnancy: L.M.P. 20th August 1919. Pregnancy ran an uneventful course until 1 a.m. on the 21st April 1920 when there was a free vaginal haemorrhage, the patient estimating the amount lost at about a pint and a half. Oozing of blood from the vagina continued, and about 11 p.m. on the same day, a second haemorrhage, less copious than the first occurred. She was admitted at 3.10 a.m. to the Royal Maternity Hospital/

Hospital on the 22nd April; the os uteri was closed and palliative treatment was adopted. On each day for three subsequent days a moderate amount of vaginal oozing went on. Labour commenced in the evening of the 25th April, a still-born child being delivered on the following morning.

Urine. 22.4.20. Albumen present in considerable amount.
23.4.20. Albumen abundantly present.
28.4.20. Albumen present in diminshed amount.
2.5.20. Only a trace of albumen present.
Unfortunately the placenta was destroyed.

Case 32.* E.R. aet. 21 years. Primigravida.

History of present pregnancy: The patient has suffered from gonorrhoea and, as an out-patient, has been attending the Ante-natal Department of the Royal Maternity Hospital for cervical swabbing. At 7 p.m. on the 6th September 1923 a considerable vaginal haemorrhage occurred for which she was admitted to hospital and a diagnosis of placenta praevia made. Labour was not in progress. Delivered 11.45/

* This patient is still (7.9.23) in the wards of the Royal Maternity Hospital; her case therefore does not strictly belong to my consecutive series; the development of albuminuria however is of such interest that I have decided to include it.

11.45 p.m. on the 7th September, i.e. about twenty-nine hours after the first onset of bleeding.

Urine: During visits to Antenatal Department the urine was repeatedly examined with negative result, the last analysis was made about four days prior to admission.

10 p.m. 6.9.23. Trace of albumen present.

11.45 " 7.9.23. Albumen abundantly present.

(No subsequent examinations have so far been made).

Placenta: The placenta was small, pale, and considerably broken up by manipulations during delivery. The praevia margin is very definitely congested and of firmer consistence than the adjacent parts of the placenta. On cut-section the contrast in appearance is well brought out.

GROUP II.

Cases of Placenta Praevia in which the urine was clear on admission but in which albuminuria was subsequently present: One case.

Case 33. Mrs S. aet. 30 years. 11-para.

Previous History: Eclampsia occurred at the birth of the first child two years ago, otherwise there is nothing of importance to record.

History of present pregnancy: L.M.P. 10th November 1921. The patient's history was featureless up till twelve days prior to admission when on the 28th June 1922 a fairly free haemorrhage occurred, the patient losing about a pint and a half of blood. The bleeding passed off but recommenced at 2 a.m. on the 9th of July; labour pains were felt shortly afterwards, but were feeble and irregular; the vagina was packed, and at 3 p.m. bipolar version was performed, the fingers being introduced at the edge of the placenta. Labour was tedious and not till 10 p.m. was delivery completed, the child being still-born. Recovery was uneventful.

Urine: Urine drawn off at 3 a.m. 9.7.22 was free from albumen.

10 p.m. 9.7.22. Trace of albumen present.

10.7.22./

10.7.22. Albumen present in considerable amount.

18.7.22. Urine now albumen-free.

Placenta: (see plate X)

On section the main mass of the placenta is normal in appearance; the praevia portion however is deeply congested and its consistence is denser than elsewhere. Almost at the extreme edge of the placenta a small localised area is firmly solidified and much lighter in colour, being in the condition of less recent infarction. This is a specially interesting specimen in view of the history of haemorrhage a fortnight prior to delivery.

Microscopic Section: Taken to include both infarcted areas. At one end of the section the appearances are those of infarction in its more fully evolved form. The villi are densely crowded together and in places neighbouring villi seem fused together by fibrin; where they remain discreet they are separated from one another by an intervillous coagulum of fairly old standing. Epithelial degeneration is marked, loss of nuclear staining in the syncytium being almost complete. The outline of the blood corpuscles in the villi and in the intervillous spaces has become indefinite. With the exception of the area of tissue showing the appearances just/

just described,the section consists mainly of placental tissue recently infarcted; great turgescence of the villous vessels is evident, and a copious intervillous, fairly fresh coagulum is present. Degenerative changes in the syncytium are less marked than is usual when the process is at this stage (compare Case 2, section No.1).

GROUP III.

Placenta Praevia combined with eclampsia: one case.

Case 34. Mrs W. aet. 38. VI-para. L.M.P. 7th July 1920.

The patient was admitted on the 6th March 1921 at 4 p.m. to Ward 35 in the Royal Infirmary with a history of vaginal haemorrhage having occurred intermittently for a month, and more or less continuously for a week. When admitted she was almost moribund from loss of blood. The os was almost fully dilated, and completely covered by placenta. The urine contained a trace of albumen, version was performed and the child and placenta slowly delivered, treatment for the bloodless state being carried out along the usual lines. At this stage the patient was very collapsed but later rallied. The improvement was maintained next day, but twenty-four hours after delivery restlessness, severe frontal headache, and epigastric pain developed and the urine showed a marked increase in the amount of albumen. Thirty-six hours after delivery a convulsive seizure occurred followed by coma from which consciousness was not regained.

Post-mortem, the kidney and liver shewed the characteristic/

characteristic appearances of eclampsia in focal necrosis and widespread interstitial haemorrhages. It is of importance to note that no changes suggestive of chronic interstitial nephritis were present in the kidney.

Placenta: The separated portion of placenta was greatly engorged and of firm consistence. Microscopically the features of recent infarction with congestion and crowding together of the villi and coagulation in the intervillous spaces were present. Apart from the praevia portion no abnormalities in the placenta were detected.

GROUP IV.

Cases of Placenta Praevia in which the urine remained albumen free throughout: eight cases.

Case 35. Mrs P. aet. 36. VI-para. L.M.P. 10th March 1919.

Clinical History: The patient was admitted to the Royal Maternity Hospital on 10th December 1920, at 6.20 p.m. with the history that about a pint of blood had been lost per vaginam three hours previously. Labour was in progress, the os being almost three-quarters dilated; lateral placental praevia was diagnosed, and version performed, delivery being completed at 10.10 p.m. on the same evening.
On the third day of the puerperium broncho-pneumonia developed and proved fatal.

Urine: The urine was examined shortly after admission and on two subsequent occasions, the analysis being negative.

Placenta: The placenta is normal in shape and consistence. A small portion of the placenta had been situated in the lower uterine segment and become separated. This part is rather more congested than normal but evidence of infarction is not convincing. In the centre of the praevia portion is a small/

small area of old pale pink infarction the size of a split pea.

Microscopic section: Taken through praevia portion cut so as to include the old infarct. The section consists largely of placental tissue apparently normal, except that unduly deep staining of the syncytial nuclei, regarded by Young as the earliest manifestation of epithelial degeneration, is very marked. Towards one end of the section is a small circumscribed area in which the villi are fused together into a more or less homogenous fibrous mass, the outline of individual villi being difficult to distinguish, and nuclear staining in the epithelial layers being almost entirely lose. Those are the appearances found in the ultimate stage of the process of infarction.

Case 36. Mrs M. aet. 39 years. XIII-para.

Previous History: Nothing of interest to note except that the twelfth labour was complicated by ante-partum haemorrhage, nature unknown.

History of present pregnancy: L.M.P. 25th July 1920. The patient's health during this pregnancy was excellent until about 8 p.m. on the 20th April 1921 when there was a slight loss of blood from the vagina;/

vagina; this ceased spontaneously, but recurred in greater amount on the following evening. On admission to the Royal Maternity Hospital at 1.30 a.m. on the 22nd April lateral placenta praevia was diagnosed. Labour was not in progress. The vagina was packed, and, at 7 p.m. on the 23rd April, the patient was delivered by version of a still-born child. Puerperium uneventful.

Urine: Examined on the day of admission and on each day for four days subsequently: analysis negative on each occasion.

Placenta: The placenta is almost bipartite, one small tongue-like process having occupied the lower uterine segment and partially covered the os uteri. Longitudinal cut-sections show the main portion of the placenta to be normal in appearance and consistence, whereas the praevia portion is markedly congested and firm to the touch; the change in colour and consistence between the healthy and diseased areas is very definite.

Microscopic sections. No.1. Taken from praevia portion. In this section the typical picture of fairly early infarction is presented; the process is probably of about forty-eight hours standing (see history) The villous vessels/

vessels are greatly engorged and in places appear to have ruptured with escape of their contents into the intervillous space. The villi are closely packed together, and early degenerative changes in their epithelium may be seen. Towards one edge of the section the placenta is looser in structure, the villi becoming more discreet and the degree of congestion less marked as normal tissue is approached.

No. 2. Taken from a congested area in the centre of the main mass of the placenta. Except that the villous vessels are rather more congested than usual normal appearances are found.

The non-appearance of albuminuria in this case, in spite of definite infarction in the placenta, is of interest; the explanation is possibly to be found in the peculiar shape of the placenta, the possible channel for the escape of noxious products of placental autolysis into the healthy placenta,and thence into the maternal circulation being essentially limited.

Case 37. Mrs B. aet. 37 years. VII-para.

L.M.P. 27th December 1919.

Clinical History: The patient was admitted to the Royal Maternity Hospital at 2.30 a.m. on the 16th September 1920 with a history of copious vaginal haemorrhage/

haemorrhage having occurred one hour previously. On admission the os admitted one finger and the margin of the placenta could be felt. The vagina was packed, and at 12.15 p.m. on the same day a still-born child was delivered by version. Puerperium uneventful.

Urine: The urine was tested on the day of admission and twice subsequently, the analysis being negative on each occasion.

Placenta:- The placenta is larger and paler than normal except in the neighbourhood of the separated area which is irregularly congested; no solidification, however, has occurred.

Microscopic section: Taken from praevia portion. No characteristic appearances of infarction formation are present. The villi are thicker and coarser, and the stroma more dense than normal. The villi are, for the most part, avascular, and what vessels are present show only a moderate degree of congestion. A patchy intervillous coagulum is present. The condition is suggestive of syphilis.

Case 38. Mrs C. aet. 34 years. VI-para.

Clinical History: L.M.P. 16th November 1919. Pregnancy ran un eventful course until the 28th July when, with the onset of labour pains, a copious vaginal haemorrhage occurred about 12 o'clock (noon). Three-quarters of an hour later the patient was admitted to the Royal Maternity Hospital in a collapsed condition. The os was three-quarters dilated, marginal placenta praevia was diagnosed, and internal version performed. At 2.15 p.m. on the same day a still-born child was delivered, the placenta being expressed manually a few minutes later. Puerperium uneventful.

Urine: The urine was examined shortly after admission and at frequent intervals thereafter, the analysis on each occasion proving negative.

Placenta: The placenta is large, and, with the exception of the praevia portion, is normal in appearance and consistence but for the presence of old or two small areas of old infarction. A film of blood-clot is loosely attached to the praevia margin. On section nothing of importance is detected; the praevia margin is so thinned out and broken that nothing definite can be said about its colour or consistence.

Microscopic Section: Taken from praevia margin.

No features of special interest are present. The section consists in the main part of healthy placental tissue. In one or two localised areas the villi are more congested than elsewhere and somewhat more closely crowded together. There is practically no blood-clot in the intervillous spaces. The appearances are too indefinite to warrant any deduction as to whether or not they may represent the earliest indications of infarction.

Case 39. Mrs B. aet. 34 years. IV-para.

Previous History: Patient has always enjoyed good health. In her obstetric history there is nothing of importance to note.

History of present pregnancy: L.M.P. 15th August 1920. The pregnancy followed an uneventful course until the morning of the 18th May 1921, when at 5.30 a.m., there was a moderately severe vaginal haemorrhage, about a pint of blood being lost. Oozing of blood from the vagina continued all day, and at 6 p.m. there was a second free haemorrhage, for which the patient was admitted to the Royal Maternity Hospital about 9 p.m. in a collapsed condition. Marginal placenta praevia was diagnosed. Labour was in progress, the os being almost fully dilated. The vagina was packed, and delivery completed by version at 11 p.m.

on/

on the same day, i.e. about eighteen hours after the first external haemorrhage occurred.

Urine: The urine contained no albumen on admission and remained albumen-free throughout.

Placenta: On inspection the praevia portion of the placenta is seen to be swollen, congested, and covered over an area a little larger than a crown piece with a thin layer of clot. On cut-section, the gradation from normal to abnormal tissue is very clearly seen, the latter being obviously of a dark plum colour and much firmer in consistence. From the size of the congested portion it is probable that in this case, the haemorrhage resulting from the separation of the praevia portion had spread upwards a short distance, separating part of the placenta attached to the uterine wall above the level of the lower uterine segment.

Microscopic sections:- No. 1. (see microphotograph No. 3). Taken through centre of praevia portion. This section shows clearly both healthy and diseased tissue, the one being fairly sharply defined from the other. Towards the foetal aspect, except for a moderate degree of congestion normal appearances are found; towards the decidual surface the typical appearances of infarction, probably/

probably of about eighteen hours standing, are observed. The villi are closely crowded together, greatly engorged with blood, and in their epithelium early degenerative changes have appeared.

No. 2. Taken from margin of congested area. Normal placental tissue is found throughout except towards the margin of the section where there are present a few indications of the condition seen in the previous section.

Case 40. Mrs C. aet. 40 years. XI-para.

Clinical History: L.M.P. 28th July 1920. Pregnancy was uneventful until the morning of the 26th April 1921 when there was a slight vaginal haemorrhage. This passed off completely, but oozing recommenced on the evening of the 29th April and at 6 a.m. on the morning of the 30th April there was a severe flooding for which the patient was admitted two hours later to hospital in a collapsed condition and a diagnosis of lateral placenta praevia made. The child was delivered by version at 3 p.m. on the day of admission; the placenta was removed manually. Puerperium uneventful.

Urine:- The urine was examined shortly after admission, and at daily intervals thereafter for four days, no albumen being present on any occasion.

Placenta:/

Placenta: The placenta has a succenturiate lobe which was apparently situated in the lower uterine segment, and has become somewhat broken up by the manipulations carried out to effect delivery. On the foetal surface a leash of vessels running from the cord to this succenturiate area is markedly dilated. Longitudinal sections cut through the whole length of placenta including the succenturiate lobe show a marked degree of engorgement of the latter. It is of a deep plum colour and of a firm consistence. Firmly adherent to the maternal surface is a film of blackish blood clot about one-eighth of an inch thick.

Microscopic section: Taken from succenturiate area (see microphotograph No.7) The appearances are those of intense infarction, of probably about four days standing (see history). The villi throughout are very greatly engorged, so that the stroma is compressed to a thin layer under the epithelium. In places the villous vessels appear to have ruptured with discharge of their contents into the intervillous spaces. In the main the villi are densely crowded together, in a few places being separated by an intervillous coagulum. The villous epithelium shows the usual early degenerative changes described elsewhere.

The/

The explanation of the non-appearance of albumen in this case in spite of definite infarction is probably similar to that offered in Case 36 (q.v.).

Case 41. Mrs L. aet. 36 years. VI-para.

Previous History: For five or six years the patient has been subject to attacks of bronchitis, otherwise her health has been satisfactory. There is nothing of importance to note with regard to her previous pregnancies or labours.

History of present pregnancy: L.M.P. 16th September 1921. Pregnancy was uneventful until the second week of May 1923 when a slight vaginal haemorrhage occurred. Similar haemorrhages recurred twice in the first week of June. For a week or two before admission to hospital the patient has felt weak, and oedema of the feet has been present; no eye-symptoms nor headaches have been complained of. No record of urinary analysis is available. At 5 p.m. on the 23rd June a severe haemorrhage occurred, about two pints of blood being lost; at 8 p.m. on the same day the patient was admitted to the Royal Maternity Hospital in a collapsed condition. The os admitted three fingers and a marginal placenta praevia could be felt.
A living child was delivered by forceps three hours after/

intervillous coagulum is present; in localised areas the villi are closely packed together; no undue congestion of the villous vessels is noted. (The appearances are not sufficiently characteristic to warrant a diagnosis of early infarction).

Case 42. Mrs S. aet. 31 years. III-para.

Previous History: Nothing of importance to note; obstetrical history featureless.

History of present pregnancy: L.M.P. ? September 1921. Except that during the early months sickness was more marked than usual, this pregnancy ran a normal course until 8.30 p.m. on the 23rd May 1922, when about a pint of blood was lost per vaginam, for which the patient was admitted two hours later to the Royal Maternity Hospital. On admission labour was in progress, and a diagnosis of lateral placenta praevia was made. Spontaneous delivery of a living child occurred at 1.15 a.m. on the 24th May.

Urine: The urine remained free from albumen throughout.

Placenta: Many areas of old infarction are seen on inspection of the maternal surface. On cut-sections being made the main mass of the placenta is found to be studded with infarcts, most of them small and old; one or two brick-red areas of infarction are also present. The placental substance is/

is rather paler than normal except for the praevia portion which shows the usual congestion, although this is not so well marked as in other cases of placenta praevia observed. No difference in consistence is detected in the separated area.

Microscopic sections: No. 1. Taken through the junction of the praevia portion with normal placenta: The section shows a considerable proportion of normal placenta; towards one end of the section is an area of recent infarction in which the villi are less densely packed together than is usual in this condition. A considerable degree of congestion of the villi is present, and coagulation in the intervillous spaces has occurred. Note the proliferation of, and deep blue staining in the syncytial nuclei, probably an indication of early epithelial degeneration.

No. 2. Taken through an old pale pink area of infarction. Contrasting this section with the preceding, note that the villi are no longer discreet but are fused by fibrin into more or less solid masses of tissue. Epithelial degeneration has reached an advanced degree, practically all evidence of nuclear staining being lost. A coagulation necrosis of the stroma cells in the villi has also occurred. (see microphotograph No.13.).

C. CASES OF ECLAMPSIA AND ALBUMINURIA UNACCOMPANIED BY ANTE-PARTUM HAEMORRHAGE.

(Twelve such cases were observed, the placenta being examined in the routine way in each. The following four cases have been selected as illustrative of certain points of importance discussed in the text).

1. Case of Eclampsia in which toxaemic symptoms were present for some weeks prior to delivery, extensive infarction in the placenta being found.

2. Case of Eclampsia in which the placenta at birth was apparently healthy.

3. Case of albuminuria of pregnancy of long-standing, extensive degenerative changes being found in the placenta at birth.

4. Case of Albuminuria of Pregnancy which, when labour ensued, had completely subsided; numerous infarcts present in the placenta at birth.

GROUP I.

Case of eclampsia in which toxaemic symptoms were present for some weeks prior to delivery, extensive infarction in the placenta being found.

Case 43. J.G. aet. 19. Primigravida. Previous health excellent. L.M.P. 30th November 1919. The patient's health during pregnancy was good until towards the middle of July 1920 when frontal headache and dizziness began to be complained of; at the same time oedema of the feet appeared, passing afterwards to the hands and face. These symptoms gradually became more pronounced and about 2 p.m. on the 5th September an eclamptic seizure occurred, six more convulsions taking place between then and the delivery of a still-born child at 4.30 p.m. on the same day. No further convulsions occurred. Puerperium uneventful.

Urine: At time of delivery the urine boiled almost solid with albumen; on the ninth day after delivery no albumen was present.

Placenta: The placenta appears deeply congested and is of irregular consistence. Cut-sections of the placenta show very extensive recent infarction of deep plum colour and consistence rather firmer/

firmer than normal. Streaks of paler, presumably normal tissue, run through the organ, and are sharply defined from the normal area. Two or three irregular areas of "brick-red" infarction are present; on the maternal surface superficial to one of these areas, a moderately old organised blood-clot about the size of a florin is firmly adherent. Numerous small old white infarcts are irregularly studded throughout the placenta.

Microscopic sections. No. 1. Taken from the centre of the deeply congested (presumably recently infarcted) area. A typical picture of infarction in its early stages is presented. The villi are moderately closely packed together; the degree of congestion of the villous vessels is so extreme that in many places the stroma is compressed into a thin layer under the epithelium. No marked degenerative changes are present in the epithelium beyond the proliferation and deep staining of the syncytial nuclei. There is a fairly recent coagulum in the intervillous spaces. (see microphotograph No.7).

No. 2. Through an area of "brick-red" infarction. Marked degenerative changes are found both in the stroma and in the epithelium of the chorionic villi, nuclear staining in the latter being largely lost;/

lost; the villi in places are reduced to mere ghost-like outlines. While there is evidence of previous great distension of the villous vessels, only a shadow of the blood corpuscles remains both in the vessels and in the intervillous spaces, the haemoglobin having been dissolved out. (see microphotograph No.14).

GROUP II.

Case of eclampsia in which the placenta at birth was apparently healthy.

Case 44. Mrs G. aet. 22 years. Primigravida.

Clinical History: L.M.P. 12th Aug. 1919. The patient's health previous to, and during the pregnancy have been excellent. Up till the time that consciousness was lost no untoward symptoms have appeared. About 2 a.m. on the 20th April 1920 labour pains commenced; about 9 a.m. on the same day an eclamptic convulsion occurred; this was followed by a second seizure two hours later. On admission at noon to the Royal Maternity Hospital, the second stage of labour was in progress, the child being born alive about one hour after admission. A third seizure occurred immediately after the birth of the child. Shortly after admission three ounces of urine were drawn off and boiled solid with albumen. Puerperium uneventful, the albumen having completely disappeared from the urine by the tenth day after delivery.

Placenta: No abnormalities are detected on surface inspection. Numerous cut-sections failed to reveal any definite abnormality beyond one or two small white infarctions situated near the placental/

placental margin. On rinsing the sections of placenta under running water a mottled appearance, (alternate ill-defined areas of pallor and congestion), such as may commonly be observed in the normal placenta, is seen.

Microscopic sections: No. 1. Taken through a congested area in the centre of the placenta.

The villi are moderately congested and are closely crowded in places. Practically no intervillous coagulation has occurred. No degenerative changes characteristic of infarction are present in the chorionic epithelium.

No. 2. Taken through a pale adjacent area. The appearances are those of normal healthy placental tissue.

GROUP III.

Case of albuminuria of pregnancy of long-standing, extensive degenerative changes being found in the placenta at birth.

Case 45.* Mrs K. aet. 32 years. Primigravida.

Clinical History: The patient"s health prior to pregnancy had been good. L.M.P. 6th April 1920. During the early months of pregnancy morning sickness was inclined to be excessive. About the thirtieth week of pregnancy symptoms of toxaemia gradually developed; headache and oedema were marked, and albumen was present in the urine. In spite of treatment the patient's condition worsened, and on the 15th November she was admitted to a nursing home under Dr Lackie's care. With careful dietetic and eliminative measures the amount of albumen decreased, although it never completely disappeared. On the 14th of December the albuminuria suddenly and rapidly increased, and the symptoms of toxaemia which had partially subsided returned in severe form. Induction of labour was decided upon, and a still-born child was delivered two days later. The puerperium was uneventful, the urine being free from albumen when the patient was discharged on the 7th January.

Placenta:/

* I am indebted to Dr Lackie for permission to include this case.

Placenta: The placenta is irregular in appearance and consistence and is obviously extensively diseased. On longitudinal sections being cut, numerous infarcts of varying age are present; some are old and pale-pink or white and of a hard consistence; others are of more recent standing, being brick-red in colour and of the consistence of liver; about one-third of the placenta is of a deep plum colour suggesting a very recent circulatory involvement. Very little normal placental tissue remains.

Microscopic sections: No. 1. Taken from the area of deep congestion:- The appearances present are those of infarction in its early stages. The bloodvessels in the chorionic villi are greatly engorged, even the most minute capillary being full of blood. Here and there one may see a villus ruptured, with extravasation of blood into the stroma of the villus or into the intervillous space. The villi are in places closely crowded together, although in this section this feature of infarction is less well marked than elsewhere. There is fairly widespread intervillous coagulation. The epithelial lining of the villi shows as yet little or no evidence of degeneration.

No. 2. Taken from an area of old (brick-red) infarction. The process is much further advanced than/

than in the section just described. The villi are closely packed together and in places appear to have become fused. The villous blood-vessels are filled for the most part with a dense coagulum, from which the haemoglobin has begun to be dissolved out. The intervillous coagulum has largely disappeared. Towards the foetal surface, at one end of the section, the texture of the tissue is more open, and here in the intervillous spaces fresh blood-clot is seen. Unduly dense nuclear staining still remains, even in those areas where fusion of neighbouring villi is most pronounced.

GROUP IV.

Case of Albuminuria of Pregnancy which when labour ensued had completely subsided; numerous infarcts present in the placenta at birth.

Case 46. Mrs S. aet. 27 years. 1-para.

Clinical History: The patient's general health has always been good. In the last week of the previous pregnancy a moderate albuminuria appeared, but passed off in the early days of the puerperium.

History of present pregnancy: L.M.P. 14th November 1921. Pregnancy was uneventful until the beginning of June 1922 when, in the routine urinary examination albumen, was found. This gradually increased in amount and was accompanied by headache and slight oedema of the face and hands. Under treatment the symptoms passed off, although the albumen never entirely disappeared. In the first week of July definite toxaemic symptoms were again present, the urine showing a considerable deposit of albumen. These symptoms again passed off, and by the beginning of August analysis of the urine was negative. The urine thereafter remained free from albumen, and a healthy child was born on the 18th of August.

Placenta: On cut-section, the placenta is found to contain two or three irregular areas of infarction. These areas are firm in consistence/

consistence and brick-red in colour. One or two small old white infarcts are also present. Towards the margin of the organ at one place is a blood cyst the size of a large pea, the placental tissue underlying which is congested and solidified.

L I T E R A T U R E.

1. Rivière, quoted from Whitridge Williams Obstetrics 1920.

2. Wells: Chemical Pathology 1907 (quoted by Holland)

3. Baer: Am. Journ. Obst. 1921, III, 245.

4. Zangemeister: Zeitschr. f. Geb. u. Gyn. 1903, Bd. 50. Arch. f. Gynak. 1908, Bd. 85..

5. Zweifel: Arch. f. Gynak, 1904, Bd. 72; 1905, Bd.76; Zentralbl.f. Gynak. 1909, Nr. 26. Zeitschr. f. Immun. 1921, XXXI, 22.

6. Ewing and Wolf: Am. Journ. Obst. 1907, LV. 289.

7. De Wesselow: Med. Science. IV. 1921, 537.

8. Hasselbach and Gammeltoft, quoted by de Wesselow.

9. Slemons: Am. Journ. Obst. 1918, LXXVII, 787.

10. Losee and van Slyke: Am. Journ. Obst. 1917, LXXV; N.Y. state med. journ. XVII I, 333.

11. Emge: Am. Journ. Obst. 1918, LXXVII,813.

12. Gscheidlin and Spiegelberg, quoted from Williams.

13. Butte, quoted by Holland.

14. Folin: Journ. Am. Med. Ass. 1917, LXIX, 1209.

15. Herter: Johns Hopkin's Hosp. Rep. 1900. IX.

16./

16. Farr and Williams, P.F.: Am. Journ. Med. Sci. 1914, 147.

17. Williams, Lisle: Journ. Am. Med. Ass. 1921, LXXVII, 1297.

19. Bogert: Journ. Biol. Chem. 1917. 32.

20. Mackenzie Wallis: Journ. Obst. & Gynaec. Brit. Emp. 1921, XXVIII, 3.

21. Löffler: Bioch. Zeitschr. 1920, CXII, 164.

22. Tweedy, Hastings: Dublin Journ. Med. Sci. 1919. CXLVIII, 186.

23. Bela Varo: quoted by de Wesselow.

24. Gessner: Zentralbl. f. Gynak. 1920, XLIV, 570.

25. Dick, C.F. & G.R.: Journ. Am. Med. Ass. 1915. LXIV, 145.

26. Talbot: Surg. Gyn. & Obst. 1919, XXVIII, 342.

27. La Vake: Journ, Lancet, 1916, XXVI, 600.

28. Lange: quoted by Nicholson.

29. Nicholson: Edin. Med. Journ., 1906, 123.

30. Pineles: Sitz. Ber. Akad. Wiss. Wien 1908, 38.

31. Erdheim: Mitteil a. d. Grenzgeb. Med. u. Chir. 1906, 632.

32. Fruhinsholz and Parisot: Gyn. et. Obst. 1921, IV, 168.

33. Fruhinsholz: Gyn. et Obst. 1922, III, 6.

34. Adam: Prog. Med. 1920, 164.

35. Walter-Wetz: Am. Journ. Obst. 1919, May.

36. Hunter: Brit. Med. Journ. 1920, 469.

37. Kark: Brit. Med. Journ. 1922, 912.

38. Young and Miller: Proc. Roy. Soc. Med. 1921. XIV. 247.

39. Westermark: Arch. f. Gynak., 1919, CX, 517.

40. Lambert & Busquet: La fonction sexuelle 1910.

41. Champy & Gley: Soc. de Biol. 1911, LXXI, 157.

42. Mackenzie Wallis & Everard Williams: Lancet 1922, 784.

43. Bory: Prog. Med. 1918, 12.

44. Paramore: Lancet 1921, II, 1147.

45. Leith Murray: Journ. Obst. & Gynaec. Brit. Emp. 1910, 242.

46. Theis: Arch. f. Gynak. XCII, 513.

47. Lockemann: Zeitschr. f. Geb. u. Gynak. 1911, LXIX, 423.

48. Gräfenburg: Zeitschr. f. Geb. u. Gynak. 1911, LXIX, 270.

49. Eisenrich: Volkmann's Samml. Klin. Vort. 1914. Mr. 694.

50. Fellander: Zeitschr. f. Geb. u. Gynak. 1911, LXVIII, 26.

51./

51. Johnstone: Journ. Obst. & Gyn. Brit. Emp. 1911, XIX, 253.

52. Holland: Journ. Obst. & Gyn. Brit. Emp. 1909, XVI, 255, 325, 384.

53. Veit: Quoted by Holland.

54. Ascoli: Quoted by Holland.

55. Weichardt: Deutsche Med. Woch. 1902, Nr. 35.

56. Liepmann: Quoted by Holland.

57. Kawasoye: Quoted by Holland.

58. Frank: Rockefeller Institute for Med. Research, 1907, Vol. VII.

59. Fordyce and Johnstone: Proc. Roy. Soc. Med. XIV. 5. 244.

60. Frankel: Gyn. Rundschr. 1909, III, 3.

61. Schenk: Zeitschr. f. Geb. u. Gynak. 1910, LXVI, No.1, 59.

62. Mathes: Zentralbl. f. Gynak, 1908, Nr. 48.

63. Englemann & Slade: Zentralbl. f. Gynak. 1908, Nr. 18.

64. Lichtenstein: Zentrbl. f. Gynak. 1909, Nr. 38.

65. Fieux and Mauriac: Anne. de Gyn. et d'Obst. 1910, VII, 67.

66. Frank & Heimann: Surg. Gyn. & Obst. XII, 454.

67. Morse: Trans. Am. Gynaec. Soc. Phila. 1919, XLIV, 103, 132.

68./

68. Obata: Journ. of Immunology, 1919, IV, III. (Quoted from Lancet leading article May 1921).

69. Dienst: Zeitschr. f. Geb. u. Gynak. 1919. (Quoted by Holland)
Arch. f. Gynak. 1908, LXXXVI, 314. (Quoted by Holland)

70. Mohr & Freund: Berlin Klin. Woch. 1908, XV.

71. Hofbauer: Zeitschr. f. Geb. u. Gynak. 1907, LXI, 200.
Zentralbl. f. Gynak. 1918, 745.

72. Schönfeld: Deutsch. Med. Woch. 1921, 270.

73. Young: Trans. Roy. Soc. Med. 1914, VII, 307.

74. Dryfuss: Biochem. Zeitschr. 1908, VII, 493.

75. Brindean & Nattan-Larrier. (Quoted by Holland).

76. Brenner: Anat. Rec. XIV, 1918, 29.

77. Cruveilhier: Ann. de Gyn. et d'Obst. 1912, IX, 486, 539.

78. Zarate: Ann. de Gyn. et d'Obst. 1914, XI, 435.

79. Williams: Obstetrics, 1920; Am. Journ. Obst. 1900, XLI, 775.

80. Fordyce and Johnstone: Edin. Med. Journ. N.S. XXX. 3. 29.

81. McNalley & Dieckmann: Am. Journ. Obst. 1922, V. 55.

82. Haffner: Gynec. et Obst. 1921, III, 81.

83. Dieulafoy: Quoted by McNalley & Dieckmann.

84. Hofmeir: Quoted by Young.

85. Scott: Am. Journ. Obst. LXXVI, 1917.

86. Muns: Quoted by Essen-Moller.

87. Essen-Moller: Trans. Internat. Med. Congress. London 1914, VIII, 25.

88. Lieven: Deutsche med. Wochenschr. 1914, 103.

89. Shaw, Fletcher: Journ. Obst. & Gyn. 1914, XXVI, 101.

90. Willson: Surg. Gyn. and Obst. Jan. 1922, 57.

91. Smyly: Trans. Roy. Acad. Med. Ireland, 1918, XXXVI, 39.

92. Couvelaire: Ann. de Gynec. et d'Obst. 1911, VIII, 591.

93. Talbot: Boston Med. and Surg. Journ. 187, 9, 315.

94. Mosher: Amer. Journ. of Obst. Dec. 1918, 803.

95. Delbet: Rev. de Chir. 1919, XXXVIII, 309.

96. Paramore: Journ. Obst. and Gyn. Brit. Emp. 1913, XXIV, 76, 149.

97. Quenu: Compt. rend. Soc. de Biol. 1918, LXXI, 850.

98. Bayliss and Cannon: Traumatic toxaemia as a factor in shock. Medical Research Committee publication.

99. Dale: Ibid.

100. Ebeler: Zentralbl. f. Gynak. X, 1916.

101. Osler: The Principles and Practice of Medicine 1919.
